

## Refine Search

### Search Results -

Terms	Documents
L1 and (antisense or ribozyme\$)	3

Database:

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L4





### Search History

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*DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=NO; OP=OR*

<u>L4</u>	l1 and (antisense or ribozyme\$)	3	<u>L4</u>
<u>L3</u>	l1 same (antisense or ribozyme\$)	1	<u>L3</u>
<u>L2</u>	melanoma adj antigen adj gene adj D1	0	<u>L2</u>
<u>L1</u>	MAGE adj D1	9	<u>L1</u>

END OF SEARCH HISTORY

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Set	Items	Description
S1	12171	CPG (S) TUMOR?
S2	0	S1 AND (BROMO CYTOSINE)
S3	1307	S1 AND (CYTOKINE? OR EXTRACT?)
S4	277	S3 AND ANTIBOD?
S5	138	S4 AND TREAT? AND (CANCER OR TUMOR?)
S6	93	RD (unique items)
S7	43	S6 AND (TREAT? (S) CANCER)

>>>KWIC option is not available in file(s): 399

**7/3,K/1 (Item 1 from file: 71)**

DIALOG(R) File 71:ELSEVIER BIOBASE

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02757601 2004234037

**Immune cell-mediated antitumor activities of GDSUB2- targeted liposomal  
c-myb antisense oligonucleotides containing CpG motifs**

Brignole C.; Pastorino F.; Marimpietri D.; Pagnan G.; Pistorio A.; Allen  
T.M.; Pistioa V.; Ponzoni M.

ADDRESS: Dr. M. Ponzoni, Differentiation Therapy Unit, Laboratory of  
Oncology, G. Gaslini Children's Hospital, Largo G. Gaslini 5,  
16147 Genoa, Italy  
EMAIL: mircoponzoni@ospedale-gaslini.ge.it  
Journal: Journal of the National Cancer Institute, 96/15 (1171-1180), 2004  
, United Kingdom  
PUBLICATION DATE: August 4, 2004  
CODEN: JNCIA  
ISSN: 0027-8874  
DOCUMENT TYPE: Article  
LANGUAGES: English SUMMARY LANGUAGES: English  
NO. OF REFERENCES: 54

Background: Expression of the c-myb proto-oncogene in neuroblastoma, the most common extracranial solid \*tumor\* of infancy, is linked with cell proliferation and differentiation. Neuroblastoma can be selectively targeted via monoclonal \*antibodies\* against the disialoganglioside (GDSUB2) \*tumor\*-associated antigen. Liposomes coated with anti-GDSUB2 \*antibodies\* (targeted liposomes) and entrapping a c-myb antisense oligonucleotide have antitumor activity. Because antisense oligonucleotides containing \*CpG\* motifs can stimulate immune responses, we evaluated the effect of \*CpG\*-containing c-myb antisense oligonucleotides encapsulated within targeted liposomes. Methods: Antisense (myb-as) and scrambled (myb-scr) control oligonucleotides with \*CpG\* motifs were encapsulated within GDSUB2-targeted and non-targeted liposomes. Two murine (nude and SCID-bg) xenograft models of neuroblastoma were established. Mice (groups of 10) were injected intravenously with various oligonucleotide and liposome formulations, and life span, long-term survival, immune cell activation, and \*cytokine\* release were measured over time. Results: \*Tumor\*-bearing mice injected with targeted liposome-\*CpG\*-myb-as or targeted liposome-\*CpG\*-myb-scr lived longer than mice in any other group, although long-term survival (i.e., more than 120 days) was obtained only in mice injected with targeted liposome-\*CpG\*-myb-as. Splenocytes isolated from mice injected with targeted liposome-\*CpG\*-myb-as contained activated macrophages, B cells, and natural killer (NK) cells, but only activated NK cells were associated with antitumor cytotoxic activity. In vivo immune cell activation was accompanied by the time-dependent increases in plasma levels of the \*cytokines\* interleukin 12 (IL-12; maximum level reached by 2 hours) and interferon gamma (IFN-gamma; maximum level reached by 18 hours) and was dependent on the oligonucleotide \*CpG\* motif. Ablation of macrophages or NK cells resulted in a loss of in vivo antitumor activity. Conclusion: Immune cell activation, involving the time-dependent activation of macrophages and NK cells, contributes to the antitumor activity of targeted liposome-\*CpG\*-myb-as against neuroblastoma and could improve the effectiveness of antitumor targeted liposomes. (c) Oxford University Press 2004, all rights reserved.

CLASSIFICATION CODE AND DESCRIPTION:  
87.4.1.9 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Antisense nucleotides  
87.4.1.13 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Drug delivery and perfusion  
87.2.8 - \*CANCER\* RESEARCH

7/3,K/2 (Item 2 from file: 71)  
DIALOG(R)File 71:ELSEVIER BIOBASE  
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02737074 2004213417

**Synergistic activation of innate immunity by double-stranded RNA and CpG  
DNA promotes enhanced antitumor activity**

Whitmore M.M.; DeVeer M.J.; Edling A.; Oates R.K.; Simons B.; Lindner D.;  
Williams B.R.G.

ADDRESS: B.R.G. Williams, Department of Cancer Biology, NB40 Lerner  
Research Institute, Cleveland Clinic Foundation, 9500 Euclid  
Avenue, Cleveland, OH 44195, United States

Journal: Cancer Research, 64/16 (5850-5860), 2004, United States

PUBLICATION DATE: August 15, 2004

CODEN: CNREA

ISSN: 0008-5472

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 73

Double-stranded RNA (dsRNA) and unmethylated \*CpG\* sequences in DNA are pathogen-associated molecular patterns of viruses and bacteria that activate innate immunity. To examine whether dsRNA and \*CpG\* DNA could combine to provide enhanced stimulation of innate immune cells, murine macrophages were stimulated with poly-rI:rC (pIC), a dsRNA analog, and \*CpG\*-containing oligodeoxynucleotides (\*CpG\*-ODN). Combined \*treatments\* demonstrated synergy in nitric oxide, interleukin (IL)-12, \*tumor\* necrosis factor alpha, and IL-6 production. Studies using neutralizing \*antibodies\* for type I interferons (IFNs), IFN-alpha and IFN-beta, indicated that nitric oxide synthase synergism is mediated by paracrine/autocrine effects of IFN-beta. In contrast, enhanced \*cytokine\* production occurred independent of type I IFN and was maintained in macrophages from IFN-alpha/beta receptor knockout mice. Cotransfection of human Toll-like receptors 3 and 9 (receptors for dsRNA and \*CpG\* DNA, respectively) into 293T cells supported synergistic activation of an IL-8 promoter reporter construct by pIC, indicating interaction of the signaling pathways in driving the synergy response. In vivo stimulation of mice with pIC and \*CpG\*-ODN demonstrated synergy for serum IL-6 and IL-12p40 levels that correlated with an enhanced antitumor effect against established B16-FSUB10 experimental pulmonary metastases. \*Treatment\* of \*tumor\*-bearing mice with pIC and \*CpG\*-ODN in combination resulted in enhanced nitric oxide synthase expression in lung tissue and enhanced up-regulation of class I major histocompatibility complex on splenic dendritic cells relative to \*treatments\* with either agent alone. In conclusion, the combined detection of viral pathogen-associated molecular patterns, i.e., dsRNA and \*CpG\* DNA, may mimic definitive viral recognition, resulting in an enhanced innate immune response that could be used for \*tumor\* vaccination or immunotherapy.

CLASSIFICATION CODE AND DESCRIPTION:

87.4.1 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Chemotherapy

87.4.11 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / \*Treatment\* Monitoring and Evaluation

86.9.3 - IMMUNOLOGY AND INFECTIOUS DISEASES

7/3,K/3 (Item 3 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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02679215

2004154996

**CEL-1000 - A peptide with adjuvant activity for Th1 immune responses**

Charoenvit Y.; Goel N.; Whelan M.; Rosenthal K.S.; Zimmerman D.H.

ADDRESS: D.H. Zimmerman, CEL-SCI Corporation, Vienna VA, 8229 Boone Blvd,  
Vienna, VA 22182, United States

EMAIL: dzimmerman@cel-sci.com

Journal: Vaccine, 22/19 (2368-2373), 2004, United Kingdom

PUBLICATION DATE: June 23, 2004

CODEN: VACCD

ISSN: 0264-410X

PUBLISHER ITEM IDENTIFIER: S0264410X04002427

DOCUMENT TYPE: Conference Paper

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 18

...1000 (derG, DGQEEKAGVVSTGLIGGG) is a small immunomodulatory peptide which delivers demonstrated protective activity in two infectious disease challenge models (HSV and malaria) and an allogenic \*tumor\* vaccine model. CEL-1000 and other activators (defensin-beta, \*CpG\* ODN, and imiquimod) of the innate immune system promote IFN-gamma-associated protective responses. CEL-1000 is an improved form of peptide G (a peptide from human MHC II beta chain second domain, aa 135-149) known to enhance immune responses of other immunogenic peptides. Since defensin-beta, \*CpG\* ODN, and imiquimod have been shown to possess adjuvant activity, we investigated the adjuvant effect of peptide G and CEL-1000 as conjugates with HIV and malaria peptides. \*Antibody\* titers and isotypes were evaluated on serum taken from select days following immunization. Results for CEL-1000 and G peptide conjugates were compared with results...

...either G or KLH-HGP-30 peptide conjugates. In another study, CEL-1000 conjugates (CEL-1000-HGP-30) demonstrated a 4-10-fold higher titer \*antibody\* response than seen with several other peptide conjugates of the same HGP-30 peptide. Improved adjuvant activity of CEL-1000 in peptide conjugates was also demonstrated by a shift in the \*antibody\* isotypes toward a Th1 response (IgG2a). The IgG2a/IgG1, ratio for G-HGP-30 HIV or KLH-HGP-30 HIV conjugates were lower than for...

...a malaria peptide conjugate (CEL-1000-SF/GF) compared to the un-conjugated peptide (SF-GF). CEL-1000 also showed adjuvant activity in an allogenic \*tumor\* vaccine model. As expected for an adjuvant, CEL-1000 or G does not induce detectable self-directed or cross reactive \*antibodies\*. CEL-1000 is currently being investigated for use as an adjuvant with conventional vaccines. It is expected that IgG2a \*antibodies\* would be preferably generated by CEL-1000 adjuvancy and could enhance in vivo clearance of antigens or pathogens. (c) 2004 Elsevier Ltd. All rights reserved.

DESCRIPTORS:

CEL-1000; \*Cytokines\*; IgG2a \*antibodies\*; Gamma interferon

CLASSIFICATION CODE AND DESCRIPTION:

...Active specific

87.4.3.2 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Active specific

87.2.11.3 - \*CANCER\* RESEARCH

7/3,K/4 (Item 4 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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02414540 2003198245

**Whole cell ELISA for measuring anti-tumour effects of immunotherapies in a mouse tumour model of ALCL**

Carstens M.; Bittner C.; Krokowski M.; Hadlak M.; Feller A.C.; Merz H.

ADDRESS: M. Carstens, St. Annen-Str. 16, D-23552 Lubeck, Germany

EMAIL: m.carstens@gmx.de

Journal: In Vivo, 17/4 (359-363), 2003, Greece

CODEN: IVIVE

ISSN: 0258-851X

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 19

...explored throughout the last century. Using the recently established TS1G6 ALCL mouse model, we compared the ability of whole cell vaccines with different combinations of \*CpG\* oligodeoxynucleotides, Diphtheria-, Pertussis- and Tetanus-vaccine (DPT) to enhance the immunogenicity of tumour cells. We have therefore developed a whole cell ELISA that detects the systemic anti-\*tumor\*-cell \*antibody\* response. \*CpG\* oligodeoxy-nucleotides can induce production of different TH1-\*cytokines\* and stimulate immune effector cells. Diphtheria-, Pertussis- and Tetanus-vaccine, injected together with irradiated \*tumor\* cells into Diphtheria-, Pertussis- and Tetanus-preimmunized mice were used to serve as a target for the host's existing memory response and thus enhance the immunogenicity of the tumour cells by induction of a local inflammation. The combined application of oligodeoxynucleotides, the vaccines and irradiated \*tumor\* cells into preimmunized mice quickly induced very high titers of tumour cell-specific \*antibody\* response. We conclude that this therapy may be a new attractive part of a tumour immunization strategy.

CLASSIFICATION CODE AND DESCRIPTION:

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immunotherapy

87.2.8 - \*CANCER\* RESEARCH

7/3,K/5 (Item 5 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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02250727 2003035572

**\*CpG\* oligonucleotides enhance the \*tumor\* antigen-specific immune response of a granulocyte macrophage colony-stimulating factor-based vaccine strategy in neuroblastoma**

Sandler A.D.; Chihara H.; Kobayashi G.; Zhu X.; Miller M.A.; Scott D.L.; Krieg A.M.

ADDRESS: A.D. Sandler, Division of Pediatric Surgery, University of Iowa,  
200 Hawkins Drive, Iowa City, IA 52242, United States

EMAIL: anthony-sandler@uiowa.edu

Journal: Cancer Research, 63/2 (394-399), 2003, United States

PUBLICATION DATE: January 15, 2003

CODEN: CNREA

ISSN: 0008-5472

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 37

**\*CpG\* oligonucleotides enhance the \*tumor\* antigen-specific immune response  
of a granulocyte macrophage colony-stimulating factor-based vaccine  
strategy in neuroblastoma**

Granulocyte macrophage colony-stimulating factor (GM-CSF)-transduced autologous \*tumor\* cells form the basis of many immunotherapeutic strategies. We tested whether combining this approach with T-helper 1 (Th-1)-like immunostimulatory \*CpG\* oligodeoxynucleotides (\*CpG\* ODNs) would improve therapeutic efficacy in an established model of murine neuroblastoma. The weakly immunogenic Neuro-2a cell line was used in syngeneic A/J mice. \*CpG\* 1826 was tested for its antitumor effect alone and as an adjuvant to Neuro-2a cells retrovirally transduced to express murine GM-CSF (GM/Neuro-2a). Three days after wild-type (WT) \*tumor\* cell inoculation, mice in different groups were s.c. vaccinated in the opposite leg with combinations of WT neuro2a, irradiated (15 Gy) WT or GM/Neuro-2a transfectants with or without \*CpG\* 1826 (200 mug). To test for the induction of memory responses, mice that rejected their \*tumor\* were rechallenged with WT Neuro-2a (1 x 10<sup>5</sup> SUP6) 7 weeks after vaccination. All of the mice in the control (unvaccinated) group died within 3 weeks after Neuro-2a inoculation. Most of the vaccinated groups had only minimal-to-modest antitumor responses, and the mice succumbed to \*tumor\*. \*Tumor\* growth was remarkably inhibited in the group of mice that received irradiated GM/Neuro-2a plus \*CpG\* and four (50%) of eight mice in this group survived \*tumor\* free. \*Tumor\*-free mice were resistant to further WT \*tumor\* cell challenge, indicating a memory response. Mechanistic studies showed that \*CpG\* alone induced a favorable Th-1-like \*cytokine\* immune response and vaccine-induced \*tumor\* cell killing was dependent on both CD4 and CD8 T cells that killed \*tumor\* cell targets by apoptosis. These results demonstrate that \*CpG\* ODNs enhanced the antitumor effect of irradiated GM-CSF secreting Neuro-2a cells. This vaccine strategy elicits a potent \*tumor\* antigen-specific immune response against established murine neuroblastoma and generates systemic neuroblastoma-specific immunity.

**CLASSIFICATION CODE AND DESCRIPTION:**

87.2.11.1 - \*CANCER\* RESEARCH...

...Tumour antigens

87.2.11.4 - \*CANCER\* RESEARCH...

...Immune response - \*antibody\*-directed responses

87.4.3.4 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immune response - \*antibody\*-directed responses

7/3,K/6 (Item 6 from file: 71)  
DIALOG(R)File 71:ELSEVIER BIOBASE  
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01265422 1999247414

**Comparison of the effect of different immunological adjuvants on the  
\*antibody\* and T-cell response to immunization with MUC1-KLH and GD3-KLH  
conjugate \*cancer\* vaccines**

Soo Kie Kim; Ragupathi G.; Musselli C.; Choi S.-J.; Yoon Sun Park;  
Livingston P.O.

ADDRESS: P.O. Livingston, Lab. of Devmtl. Tumor Vaccinology, Memorial  
Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021  
, United States

Journal: Vaccine, 18/7-8 (597-603), 1999, United Kingdom

CODEN: VACCD

ISSN: 0264-410X

PUBLISHER ITEM IDENTIFIER: S0264410X99003163

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 20

**Comparison of the effect of different immunological adjuvants on the  
\*antibody\* and T-cell response to immunization with MUC1-KLH and GD3-KLH  
conjugate \*cancer\* vaccines**

While the importance of immunological adjuvants for optimal induction of \*antibody\* and T-cell responses against \*tumor\* antigens is clear, the relevant potency of different adjuvants is not clear. We have screened 19 different immunological adjuvants with KLH conjugate vaccines containing the two human \*cancer\* antigens (MUC1 peptide and GD3 ganglioside) in the mouse. ELISA assays for IgM and IgG \*antibody\* responses as well as proliferation and \*cytokine\* release (IFN-gamma and IL-4) for T-cell responses were performed. Six adjuvants stood out as being especially effective for induction of IgM and IgG \*antibodies\* against both MUC1 and GD3: QS-21, TiterMax, MoGM-CSF, MPL/DETOX and \*CpG\* ODN. Of these QS-21, MPL/DETOX and MoGM-CSF were uniformly effective at inducing potent proliferation and potent IFN-gamma and IL-4 responses against KLH while TiterMax and \*CpG\* ODN generated potent IFN-gamma responses but less potent proliferation or IL-4 release. Overall, as in our previous experience, QS-21 was the most...

...clear evidence for induction of T-cell immunity against either GD3 or MUC1 with any of the adjuvants. There was a strong correlation between the \*antibodies\* induced against MUC1 and GD3 with different immunological adjuvants and the strength of the IFN-gamma release against KLH. This suggests that the primary role...

...in the context of these conjugate vaccines may be induction of higher levels of T-cell immunity against KLH, which then leads to higher levels \*antibody\* against the conjugated antigens.

**CLASSIFICATION CODE AND DESCRIPTION:**

...Tumour Immunotherapy

87.3.1 - \*CANCER\* RESEARCH...

...Classification and Prognostic Indicators

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immunotherapy



87.4.11 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / \*Treatment\* Monitoring and Evaluation

7/3,K/7 (Item 7 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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00719535 97224422

**Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif are effective as immune adjuvants in \*tumor\* antigen immunization**

Weiner G.J.; Liu H.-M.; Wooldridge J.E.; Dahle C.E.; Krieg A.M.

ADDRESS: G.J. Weiner, C32 General Hospital, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, United States

EMAIL: george-weiner@uiowa.edu

Journal: Proceedings of the National Academy of Sciences of the United States of America, 94/20 (10833-10837), 1997, United States

PUBLICATION DATE: 19970000

CODEN: PNASA

ISSN: 0027-8424

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 24

**Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif are effective as immune adjuvants in \*tumor\* antigen immunization**

Recent advances in our understanding of the immune response are allowing for the logical design of new approaches to \*cancer\* immunization. One area of interest is the development of new immune adjuvants. Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif (\*CpG\* ODN) can induce production of a wide variety of \*cytokines\* and activate B cells, monocytes, dendritic cells, and NK cells. Using the 38C13 B cell lymphoma model, we assessed whether \*CpG\* ODN can function as immune adjuvants in \*tumor\* antigen immunization. The idiotype served as the \*tumor\* antigen. Select \*CpG\* ODN were as effective as complete Freund's adjuvant at inducing an antigen-specific \*antibody\* response but were associated with less toxicity. These \*CpG\* ODN induced a higher titer of antigen-specific IgG2a than did complete Freund's adjuvant, suggesting an enhanced TH1 response. Mice immunized with \*CpG\* ODN as an adjuvant were protected from \*tumor\* challenge to a degree similar to that seen in mice immunized with complete Freund's adjuvant. We conclude that \*CpG\* ODN are effective as immune adjuvants and are attractive as part of a \*tumor\* immunization strategy.

CLASSIFICATION CODE AND DESCRIPTION:

87.2.11 - \*CANCER\* RESEARCH...

...Immunology

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* /

7/3,K/8 (Item 1 from file: 98)

DIALOG(R)File 98:General Sci Abs/Full-Text

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04755409 H.W. WILSON RECORD NUMBER: BGS02005409 (USE FORMAT 7 FOR

FULLTEXT)

**Molecular pathogenesis of lung \*cancer\*.**

Zochbauer-Muller, Sabine

Gazdar, Adi F; Minna, John D

Annual Review of Physiology v. 64 (2002) p. 681-708

SPECIAL FEATURES: bibl il ISSN: 0066-4278

LANGUAGE: English

COUNTRY OF PUBLICATION: United States

WORD COUNT: 13622

(USE FORMAT 7 FOR FULLTEXT)

**Molecular pathogenesis of lung \*cancer\*.**

**ABSTRACT:** Lung \*cancer\* is the most common cause of \*cancer\* death in the United States, killing more than 156,000 people every year. In the past two decades, significant progress has been made in understanding the molecular and cellular pathogenesis of lung \*cancer\*. Abnormalities of proto-oncogenes, genetic and epigenetic changes of \*tumor\* suppressor genes, the role of angiogenesis in the multistage development of lung \*cancer\*, as well as detection of molecular abnormalities in preinvasive respiratory lesions, have recently come into focus. Efforts are ongoing to translate these findings into new clinical strategies for risk assessment, chemoprevention, early diagnosis, \*treatment\* selection, and prognosis and to provide new targets and methods of \*treatment\* for lung \*cancer\* patients. All these strategies should aid in reducing the number of newly diagnosed lung \*cancer\* cases and in increasing the survival and quality of life of patients with lung \*cancer\*. Reprinted by permission of the publisher.

**TEXT:**

Key Words \*tumor\* suppressor gene, allele loss, methylation, angiogenesis, preneoplasia

1 Abbreviations: NSCLC, non-small cell lung \*cancer\*; SCLC, small cell lung \*cancer\*; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; NMB, neuromedin B; NMBR, neuromedin B receptor; BRS-3, bombesin receptor subtype 3; IGF, insulin-like growth factor; PDGR, platelet-derived growth factor; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; TSG, \*tumor\* suppressor gene; LOH, loss of heterozygosity; FHIT gene, fragile histidine triad gene; RARb, retinoic acid receptor b; p14, p14ARF; RB, retinoblastoma gene; CDK, cyclin-dependent...  
...death-associated protein kinase; ECAD, E-cadherin; GSTP1, glutathione-S-transferase P1; p15, p15INK4b; VEGF, vascular epithelial growth factor; RER, replication error repair

**INTRODUCTION**

Lung \*cancer\* is one of the most prevalent and lethal cancers in the world. In the United States about 156,000 people died because of lung \*cancer\* last year, which represents 28[percent] of all \*cancer\* deaths (1). Although the rate of lung \*cancer\* deaths for males is decreasing in the United States, the mortality associated with lung \*cancer\* among women continues to increase (2). Cigarette smoking is the main risk factor for lung \*cancer\*, accounting for about 90[percent] of the cases in men and 70[percent] of the cases in women (3, 4). Exposures to other environmental and occupational respiratory carcinogens may be interactive with cigarette smoking and thus also influence lung \*cancer\* incidence. Nevertheless, prevention of smoking initiation and increased smoking cessation remain the best long-term methods to prevent lung \*cancer\* development. The major histologic types of lung \*cancer\* are non-small cell lung cancers

(NSCLC), (FN1) which represent about 80[percent] of lung cancers and are divided into squamous cell carcinoma, adenocarcinoma (including...

...cell carcinoma and mixed types, and small cell lung cancers (SCLC), which represent about 20[percent] of lung cancers. Development of metastases when the primary \*tumors\* are still small, coupled with lack of methods for early diagnosis and of systemic therapies with great efficacy to deal with micrometastatic disease are the main reasons why the prognosis of lung \*cancer\* patients is still poor, with over-all 5-year survival rates of about 14[percent] (5). Thus new methods for early detection and identification of smokers at greatest risk for developing lung \*cancer\*, such as spiral-computed tomography screening for early lung cancers, biomarkers for lung \*cancer\* risk assessment, new approaches for lung \*cancer\* prevention (chemo-prevention), and new drugs based on rational targets, are necessary and need to be developed. In this review we summarize the advances that have been made in understanding the molecular and cellular biology of lung \*cancer\* over the recent years (major molecular abnormalities summarized in Table 1). It is hoped that these new findings will result in novel approaches for prevention and early detection of lung \*cancer\* and new effective \*treatment\* strategies for lung \*cancer\* patients.

AUTOCRINE AND PARACRINE SYSTEMS: GROWTH FACTORS AND THEIR RECEPTORS  
Many growth factors and their receptors are expressed by lung \*cancer\* cells or adjacent normal cells leading to the development of several autocrine or paracrine growth stimulatory loops (6). One of the best-characterized autocrine systems...

...in NSCLCs, whereas the expression of GRPR and BRS-3 is less frequent (9). Also the ligands for these receptors are often expressed in lung \*cancer\* cells leading to potential self-stimulatory (autocrine) loops. The NMB gene is expressed in 100[percent] of SCLCs and NSCLCs (10). Approximately 20-60[percent]...

...two expressed copies of the X-linked GRPR gene in females may be a factor in the increased susceptibility of women to tobacco-induced lung \*cancer\*. Blocking this system with \*antibodies\* or receptor antagonists results in inhibition of \*tumor\* growth in model systems; this concept is being explored as a new therapeutic avenue (13). Other peptides with potential autocrine growth function in lung \*cancer\* are insulin-like growth factors (IGF) I and II (14). Wu et al. (15) tested the hypothesis that accumulation of genetic damage is dependent on...

...blood levels of IGF-I and the molar ratio of IGF-I/IGF-binding protein-3 were higher in patients with advanced or poorly differentiated \*cancer\* than in patients with early or well-differentiated cancers.

The c-erbB-1 proto-oncogene encodes the receptor for the epidermal growth factor (EGFR), which regulates epithelial proliferation and differentiation and is activated in lung \*cancer\* cells by overexpression (16, 17). The EGFR gene was found to be overexpressed in 13[percent] of NSCLCs (18), and EGFR protein expression by \*tumors\* seems to be a poor prognosis risk factor in NSCLC patients (...185 kDa (p 185neu), is another growth factor receptor and is frequently expressed in NSCLCs, but not in SCLCs (20, 21). Using an anti-p185HER2 \*antibody\*, inhibition of human lung \*cancer\* cell line growth has been demonstrated (22), whereas anti-EGFR \*antibodies\* can inhibit the growth of human \*tumor\* cell lines overexpressing EGFR. The use of humanized monoclonal anti-HER2 \*antibody\* (Herceptin) has been tested in breast \*cancer\* \*treatment\* with promising results and is also being evaluated clinically in lung \*cancer\*.

Additionally, several new drugs have been developed that block the tyrosine kinase activity of these receptors, which leads to \*tumor\* growth inhibition in preclinical models; these drugs have also recently gone into clinical trials.

The hepatocyte growth factor (HGF) and its receptor comprise another growth factor/receptor complex that may play a role in lung \*cancer\* development. HGF, which stimulates epithelial cells to proliferate, move, and carry out differentiation programs, is expressed in many NSCLCs (23, 24) where it is associated...

...The receptor for HGF is encoded by the oncogene MET, which is expressed in normal lung epithelium, SCLCs, and NSCLCs (23, 24, 26). Thus these \*tumor\* cells have both the receptor and the ligand for this growth factor.

Data in the literature concerning the expression of estrogen and progesterone receptors in human lung \*cancer\* are discordant. Di Nunno et al. (27) did not find estrogen or progesterone receptor expression in a large series of NSCLC samples, whereas Su et...

...by p53. Forced overexpression of oncogenic MYC or RAS in fibroblasts can lead to apoptosis in the face of nutrient deprivation. It is likely that \*tumor\* cells over-express BCL-2 to overcome apoptotic signals from MYC and RAS expression. Immunohistochemical studies have shown that BCL-2 protein is expressed frequently...

...expression is higher in squamous cell carcinomas than in adenocarcinomas (37). Of interest, some studies demonstrate a survival benefit for patients with BCL-2-positive \*tumors\* (37-40) while others do not confirm this finding (41). A higher response rate to chemotherapy was observed for BCL-2-positive \*tumors\* compared with BCL-2-negative \*tumors\*, suggesting that BCL-2 expression reflects a higher susceptibility to cytotoxic \*treatment\* (38). Antisense BCL-2 drugs, which block translation of BCL-2 protein in \*tumor\* cells, will soon be tested in clinical trials. These drugs may work either alone or by increasing a \*tumor\* cell response to standard chemotherapy and radiotherapy.

#### NOTCH-3

Notch-3 is located on chromosome 19p in a region that was found to be translocated...

...associated with chromosome 19p translocation (42). This finding is of particular interest because it demonstrates that a specific chromosome translocation occurs in a common epithelial \*cancer\* and activates a gene not previously implicated in lung \*cancer\*.

#### AIS

AIS (amplified in squamous cell carcinoma) is a p53 homologue located on the distal long arm of chromosome 3 with multiple protein products (p40...

...analysis revealed frequent amplification of this gene locus in primary lung squamous cell carcinomas, and protein overexpression was observed in lung squamous cell carcinomas and \*tumors\* known to harbor a high frequency of p53 mutations, suggesting that AIS plays an oncogenic role in lung squamous cell carcinomas (43). Circulating anti-p40 (AIS) \*antibodies\* have been detected in the sera of respiratory tract \*cancer\* patients, but the presence or absence of AIS \*antibodies\* were independent of other clinicopathological characteristics of these patients (44).

#### CHROMOSOMAL SITS OF FREQUENT ALLELE LOSS AND \*TUMOR\* SUPPRESSOR GENES

(TSGs)

According to Knudson's two-hit hypothesis (45), loss of function of TSGs requires that both alleles have to be inactivated. One...

...region referred to as allele loss or loss of heterozygosity (LOH) (30, 46). Thus consistent LOH for genetic markers at a given locus in many \*tumors\* is strong evidence for the presence of one or more TSGs in that region. Recently, a genome-wide high-resolution search of LOH was performed ...

...carcinomas and primary adenocarcinomas was also investigated in the study by Wistuba et al. (48) using 19 polymorphic microsatellite markers at 12 chromosomal regions. Each \*tumor\* type had a characteristic pattern of allelic loss, and the bronchial epithelium accompanying SCLCs showed a much higher frequency of LOH compared with squamous cell...

...by Sanchez-Cespedes et al. (49) reported a much higher frequency of widespread chromosomal abnormalities in lung adenocarcinomas from smokers compared with infrequent changes in \*tumors\* arising in nonsmokers.

So far, 3p allele loss has been shown to be the most frequent molecular alteration in lung cancers (47, 50, 51). However, 3p allele loss occurs not only in \*tumors\* but also in the normal epithelium of smokers without lung \*cancer\*, and hyperplasias, dysplasias, and carcinoma in situ in the respiratory epithelium accompanying lung cancers, suggesting that it is an early change in the multistep pathogenesis of lung \*cancer\* (51-53). A high-resolution 3p LOH study in primary lung \*tumors\* and preneoplastic/preinvasive lesions using a panel of 28 microsatellite markers demonstrated a progressive increase in the frequency and size of 3p allelic loss regions...

...transcripts that are produced by alternative promoter selection and alternative mRNA splicing. mRNA expression of one of these transcripts, RASSF1A, is frequently lost in lung \*cancer\*. The major mechanism for inactivating RASSF1A is by aberrant methylation of its promoter region turning off its expression; inactivation of RASSF1A by mutation is rare (56-58). Additionally, the study by Burbee et al. (57) shows that patients whose \*tumors\* are methylated for RASSF1A have a shorter overall survival rate than patients whose \*tumors\* are not methylated for RASSF1A. Thus these data strongly support the candidacy of RASSF1A as a TSG that plays a major role in the pathogenesis of lung \*cancer\*. The FHIT (fragile histidine triad) gene, a candidate TSG that spans the FRA3B common fragile site at 3p14.2, was found to be frequently abnormal in lung \*cancer\* (59, 60). Aberrant FHIT transcripts were detected in 80[percent] of SCLC and 40[percent] of NSCLC specimens (59, 60), and absent FHIT protein expression ...

...more frequently in smokers than in nonsmokers, suggesting that FHIT is a molecular target of tobacco smoke carcinogens (61). Recently, aberrant methylation of the 5' \*CpG\* island of the FHIT gene was shown to be an important mechanism for silencing this gene in lung \*cancer\* (63). Transfection of a wild-type copy of FHIT into lung \*cancer\* cells can reverse the malignant phenotype and induce \*tumor\* cell apoptosis (64, 65); this suggests that FHIT overexpression could serve as a future therapeutic approach.

The retinoic acid receptor b-2 (RARb) gene located at 3p24 has been intensively studied in lung \*cancer\* and found to have defective function, thus making it a candidate TSG. This is particularly important given the interest in using retinoids as chemoprevention agents for lung \*cancer\*. RARb is a key retinoid receptor that mediates growth control responses, and considerable evidence suggests that RARb abnormalities exist in lung

cancers (66-69). A lung \*cancer\* cell line Calu-1 (70). Frequent loss of RARb mRNA expression has been described in both primary NSCLCs and bronchial biopsy specimens from heavy smokers...

...screening for homozygous deletions, a homozygously deleted region on chromosome 2q has been identified (84). This region harbors the lipoprotein receptor-related protein-deleted in \*tumors\* (LRP-DIT) gene. Homozygous deletions in LRP-DIT were detected in 17[percent] of NSCLC cell lines, and expression of only abnormal transcripts missing parts...

...Recently, the TSLC1 gene has been identified at chromosome 11q23.2 (85). This region is of particular interest because LOH occurs frequently and, in addition, \*tumorigenicity\* of A549 lung \*cancer\* cells can be suppressed by this region. Moreover, loss of TSLC1 expression was observed frequently in NSCLCs, and aberrant methylation of the promoter region has...

...isoform of the A subunit of the serine/threonine protein phosphatase 2A (PP2A), was found to be altered by mutations in lung, colon, and breast \*cancer\*, thus suggesting it as a putative TSG (86).

#### P53

The p53 gene, located at chromosome region 17p13.1, encodes a 53-kDa nuclear protein. This...

...genes results in apoptosis, cell cycle arrest, and DNA repair. Mutations of the p53 gene comprise some of the most common genetic changes associated with \*cancer\* and cause loss of \*tumor\* suppressor function and loss of ability to induce apoptosis. The prevalent type of point mutations is a GC to TA transversion causing missense mutations. This...

...in protein studies, and the incidence of p53 overexpression and mutations in adenocarcinomas was significantly lower than that in squamous cell carcinomas.

As a new \*treatment\* approach, p53 has been introduced into clinical trials with retroviral and adenoviral gene therapy delivered directly into \*tumors\* with initially promising antitumor responses (100). A recent study investigated the additional benefit from adenoviral p53 gene therapy directly injected into \*tumors\* in patients undergoing first-line chemotherapy for NSCLC (101). However, no differences in response rates or survival were observed between the group \*treated\* with additional p53 gene therapy and the group \*treated\* with chemotherapy alone. The successful systemic delivery of p53 by liposomes has been shown recently in lung \*cancer\* (102) and needs to be investigated further for \*treatment\* of primary and disseminated lung \*cancer\*. In addition, vaccine trials using mutant p53 peptides have been completed (103).

#### THE P16INK4-CYCLIN D1-CDK4-RB PATHWAY

p16INK4 (p16) was mapped to the...binding to the MDM2-p53 complex, it prevents p53 degradation, thereby leading to p53 activation. Loss of p14 expression was more frequently found in lung \*tumors\* with neuroendocrine features (110). However, aberrant methylation of the p14 promoter region did not occur frequently in NSCLCs (108).

The other key component in this...

...which is found in [similar]90[percent] of all lung cancers. However, it is uncommon to have both RB and p16 inactivated in the same \*tumor\*. Loss of RB function can occur by deletions, mutations, or splicing abnormalities. Abnormalities of the RB protein are found in more than 90[percent] of...

...grading and development of metastasis in lung cancers (118). Recently, Claudio et al. (119) reported a high frequency of RB2/p130 mutations in primary lung \*tumors\*. Retrovirus-mediated delivery of wild-type RB2/p130 to a lung \*tumor\* cell line potently inhibited \*tumorigenesis\*, suggesting that RB2/p130 may be a candidate for gene therapy trials for lung \*cancer\*.

#### APC (ADENOMATOUS POLYPOSIS COLI) GENE/WNT PATHWAY

The APC gene encodes a large protein with multiple cellular functions and interactions, including roles in signal transduction...

...APC has been frequently observed in primary lung cancers, and aberrant methylation is the most important mechanism for inactivating expression of this gene in lung \*cancer\* (121). With loss of APC expression, the wnt-signaling pathway is constitutively turned on, resulting in accumulation of b-catenin as the result of wnt...

...and cyclin D1, both of which regulate cell cycle progression. Although this could also occur by b-catenin mutations, these mutations are rare in lung \*cancer\*.

The occurrence of mutations in the PTEN/MMAC1 gene, which is located at the chromosomal region 10q23.3, has been investigated in a large number ...

...that genetic abnormalities of this gene are only involved in a relatively small subset of lung cancers.

#### ABERRANT PROMOTER METHYLATION

Aberrant methylation of normally unmethylated \*CpG\*-rich areas, also known as \*CpG\* islands that are located in or near the promoter region of many genes, has been associated with transcriptional inactivation of TSGs in human \*cancer\* (105, 123). Methylation serves as an alternative to the genetic loss of a TSG function by deletion or mutation. As discussed above, several genes are frequently methylated in primary lung \*tumors\* including the genes adenomatous polyposis coli (APC), retinoic acid receptor b-2 (RARb), CDH13 (H-cadherin), fragile histidine triad (FHIT), RASSF1A, tissue inhibitor of metalloproteinase...

...death-associated protein kinase (DAPK) (56-58, 63, 74, 105, 108, 121, 124-128) (Table 2). A significantly shorter disease-free survival for patients whose \*tumors\* were methylated for DAPK was reported by Tang et al. (128), and Burbee et al. (57) found a shorter overall survival for patients whose tumors were methylated for RASSF1A. Methylated DNA sequences can be detected in primary lung cancers, circulating in serum DNA from lung \*cancer\* patients, in sputum samples prior to the onset of invasive lung \*cancer\*, as well as in precursor lesions for lung carcinomas (106, 129, 130). These findings indicate that aberrant methylation can develop during the preneoplastic process and thus may serve as a potential biomarker for early diagnosis of lung \*cancer\*, as well as in following disease load. Determining the methylation status of certain genes in bronchial biopsies, bronchioloalveolar washings, and sputum samples from high-risk individuals such as heavy smokers is being tested as a marker for lung \*cancer\* risk assessment. Aberrant methylation can be reversed in vitro by drugs that block methylation such as 5-aza-2'-deoxycytidine, which results in gene re-expression and \*tumor\* growth inhibition (63, 74). Histone deacetylase inhibitors also can reverse the methylation status of genes and frequently are additive or synergistic with 5-aza-2'-deoxycytidine. Because of the frequency of \*tumor\*-acquired methylation, clinical trials with demethylating drugs such as 5-aza-2'-deoxycytidine, with or without histone deacetylase inhibitors, are being developed (131).

#### \*TUMOR\* ANGIOGENESIS

Angiogenesis is important in neoplastic development and progression because both \*tumor\* growth and metastatic dissemination of \*tumor\* cells depend on vascular support (132). An increasing number of angiogenic factors, i.e., inducers and inhibitors regulating endothelial cell proliferation and migration, have been identified (132-134). Angiogenic factors affect vasculature formation, growth patterns, and vascular permeability, modulate host response, and influence \*tumor\* invasion, metastasis, and prognosis. \*Tumor\* cells and their precursor cells are able to secrete angiogenic substances that depend on certain factors including hypoxia and alterations in dominant and recessive oncogenes...

...prime regulators of both physiological and pathological angiogenesis (134). So far, two receptors for VEGF, which are selectively expressed in endothelium, have been characterized, and \*antibodies\* have been developed that can block the interaction between VEGF and its ...139). This fact is important because dendritic cells are important for antigen presentation and suggest that inadequate function may be responsible for the escape of \*tumors\* from the host immune system. VEGF expression in NSCLCs was significantly associated with new vessel formation and was an adverse prognostic factor in these patients (140). Koukourakis et al. (141) investigated the activated microvessel density in early operable NSCLCs and found it significantly higher in the invading front of the \*tumors\* and in the normal lung adjacent to the \*tumors\* compared with normal lung distal to the \*tumor\* or the inner \*tumor\* areas. These results suggest that activated microvessel density serves as an independent prognostic factor in NSCLC patients. Upregulation of platelet-derived endothelial cell growth factor...

...the microvessel count was a highly significant adverse predictor of both overall and disease-free survival in patients with NSCLC, suggesting that the evaluation of \*tumor\* angiogenesis may be useful in the postsurgical staging of NSCLC patients to identify subsets of patients who may benefit from adjuvant \*treatment\* studies. New \*treatment\* approaches directed against angiogenic factors or their receptors are being investigated in clinical trials in lung \*cancer\*. These include humanized monoclonal anti-VEGF \*antibodies\*, anti-VEGF receptor \*antibodies\*, and drugs blocking the VEGF receptors' tyrosine kinase activity essential for their function.

#### TOBACCO SMOKE CARCINOGENS

Tobacco smoke is responsible for about 90[percent] of all cases of lung \*cancer\*. The three major classes of carcinogens in tobacco smoke are the polycyclic hydrocarbons such as benzo(a)pyrene, nitrosamines, and aromatic amines (144). The carcinogenic...

...which may result in DNA misreplication and mutation. A significant association between the level of benzo(a)pyrene-induced DNA adducts and risk for lung \*cancer\* has been reported and suggests that subjects sensitive to benzo(a)pyrene-induced DNA damage may have a suboptimal ability to remove benzo(a)pyrene-DNA adducts. These subjects are thus susceptible to tobacco carcinogen exposure and may be at increased risk of developing lung \*cancer\* (145).

#### ALTERATIONS IN SMOKE-DAMAGED RESPIRATORY EPITHELIUM

Lung cancers are believed to arise after a series of progressive pathological changes in the respiratory epithelium, and...



...areas of dysplasia and in atypical alveolar hyperplasia (147). LOH at chromosomal regions 8p and 9p occurs early in the multistage development of invasive lung \*cancer\*; however, LOH at 3p is the earliest and most frequent event (51, 52, 148, 149). Allele loss at 8p21-23, commenced at the hyperplasia/metaplasia stage, was seen in 65[percent] of smokers without \*cancer\* and persisted for up to 48 years after smoking cessation. Similar to LOH found at chromosome 3p, there was also a progressive increase in the ...

...size of allele loss with increasing severity of histopathologic preneoplastic changes. LOH was also detected in plasma DNA from individuals at high risk of lung \*cancer\* (150). Recently, aberrant methylation of certain genes has been linked to early stages of respiratory carcinogenesis. Belinsky et al. (129) reported that aberrant methylation of ...

...of neoplasia (151), and p16 methylation, p53 mutations, KRAS mutations, and microsatellite instability were detected in bronchoalveolar lavage fluid from patients with early-stage lung \*cancer\* (152). Additionally, aberrant methylation of FHIT has been found in the smoking-damaged bronchial epithelium from heavy smokers without \*cancer\* (63). A high frequency of mitochondrial DNA (mtDNA) mutations have been described in various malignant \*tumors\* including lung \*cancer\* (153). The mutated mtDNA was detectable in bronchoalveolar lavage fluids, suggesting that it may serve as a powerful molecular marker for detection of lung \*cancer\*. The functional significance of such mitochondrial changes is currently unknown.

The fact that specific alterations can be detected in preneoplastic/preinvasive lesions suggests that these abnormalities may be useful as biomarkers for lung \*cancer\*. These biomarkers could be used to identify individuals at high risk for developing lung \*cancer\*, monitor the efficacy of lung \*cancer\* chemoprevention trials, diagnose lung \*cancer\* in early stages, and monitor the efficacy of lung \*cancer\* therapies. Additionally, study of biomarkers in \*tumors\* could identify patients with different prognoses and allow tailoring of therapy. Samples used to test for biomarkers for risk assessment have to be obtainable in...

...in about 35[percent] of SCLCs and 22[percent] of NSCLCs (30). Thus microsatellite alterations have been tested as molecular biomarkers for early detection of \*cancer\* cells in sputum and bronchial washings (152, 154). In other human \*tumors\* such as colon \*cancer\*, the replication error repair (RER) phenotype results in "laddering" of short tandem repeat sequences associated with inherited or acquired mutations in DNA mismatch repair genes such as MSH2 and hMLH1 (30). However, this RER phenotype or mutations in these genes have not been found in lung cancers. Lung \*tumors\* with microsatellite alterations at selected tetranucleotide repeats have a high frequency of p53 mutations and do not display a phenotype consistent with defects in mismatch repair (155). The molecular abnormalities underlying such microsatellite alterations in lung \*cancer\* are unknown.

#### TELOMERASE ACTIVITY

The ends of human chromosomes (telomeres) contain the hexameric TTAGGG tandem repeats. During normal cell division, the absence of telomerase activity is associated with progressive telomere shortening, leading to cell senescence and normal cell mortality (30). On the contrary, germ cells, some stem cells, and most \*cancer\* cells have telomerase activity that results in replacing the hexameric repeats, therefore leading to potential cellular immortality (30). The majority of SCLCs and about 80... ..and advanced stage in NSCLCs (157). Because of this, anti-telomerase drugs are being developed as new therapeutics for a variety of cancers

including lung \*cancer\*. Telomerase components are activated in the latent preneoplastic stages of lung \*cancer\*. The mechanism for re-expression of the catalytic component hTERT or the RNA component of telomerase in \*tumors\* is currently unknown. Normal epithelial cells can be immortalized and transformed to malignancy by the combination of hTERT, SV40 T antigen, and a mutated RAS gene (158).

#### NEUROENDOCRINE PHENOTYPE OF LUNG \*TUMORS\*

The classification of neuroendocrine (NE) lung \*tumors\* includes carcinoids and SCLCs and has been enlarged with a new entity, the large cell NE carcinomas (LCNEC) (159). NE lung \*tumors\* share certain morphological, ultrastructural, immunohistochemical, and other molecular characteristics that sustain their NE phenotype (e.g., NE secretory granules at electron microscopy, NE markers at immunohistochemistry) (159). Specific NE markers include chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM). NE lung \*tumors\* appear to be epithelial \*tumors\* characterized by their preferential NE differentiation but retain their propensity to follow multidirectional differentiation pathway. The derivation of all histologic types of lung \*cancer\* from a common endodermal stem cell is likely to be responsible for the frequent multidirectional differentiation in lung \*tumors\*. However, this stem cell has not yet been identified.

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Set	Items	Description
S1	12171	CPG (S) TUMOR?
S2	0	S1 AND (BROMO CYTOSINE)
S3	1307	S1 AND (CYTOKINE? OR EXTRACT?)
S4	277	S3 AND ANTIBOD?
S5	138	S4 AND TREAT? AND (CANCER OR TUMOR?)
S6	93	RD (unique items)
S7	43	S6 AND (TREAT? (S) CANCER)

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**7/3,K/1 (Item 1 from file: 71)**  
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**Immune cell-mediated antitumor activities of GDSUB2- targeted liposomal c-myb antisense oligonucleotides containing CpG motifs**  
Brignole C.; Pastorino F.; Marimpietri D.; Pagnan G.; Pistorio A.; Allen T.M.; Pistioa V.; Ponzoni M.

ADDRESS: Dr. M. Ponzoni, Differentiation Therapy Unit, Laboratory of  
Oncology, G. Gaslini Children's Hospital, Largo G. Gaslini 5,  
16147 Genoa, Italy  
EMAIL: mircoponzoni@ospedale-gaslini.ge.it  
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Background: Expression of the c-myb proto-oncogene in neuroblastoma, the most common extracranial solid \*tumor\* of infancy, is linked with cell proliferation and differentiation. Neuroblastoma can be selectively targeted via monoclonal \*antibodies\* against the disialoganglioside (GDSUB2) \*tumor\*-associated antigen. Liposomes coated with anti-GDSUB2 \*antibodies\* (targeted liposomes) and entrapping a c-myb antisense oligonucleotide have antitumor activity. Because antisense oligonucleotides containing \*CpG\* motifs can stimulate immune responses, we evaluated the effect of \*CpG\*-containing c-myb antisense oligonucleotides encapsulated within targeted liposomes. Methods: Antisense (myb-as) and scrambled (myb-scr) control oligonucleotides with \*CpG\* motifs were encapsulated within GDSUB2-targeted and non-targeted liposomes. Two murine (nude and SCID-bg) xenograft models of neuroblastoma were established. Mice (groups of 10) were injected intravenously with various oligonucleotide and liposome formulations, and life span, long-term survival, immune cell activation, and \*cytokine\* release were measured over time. Results: \*Tumor\*-bearing mice injected with targeted liposome-\*CpG\*-myb-as or targeted liposome-\*CpG\*-myb-scr lived longer than mice in any other group, although long-term survival (i.e., more than 120 days) was obtained only in mice injected with targeted liposome-\*CpG\*-myb-as. Splenocytes isolated from mice injected with targeted liposome-\*CpG\*-myb-as contained activated macrophages, B cells, and natural killer (NK) cells, but only activated NK cells were associated with antitumor cytotoxic activity. In vivo immune cell activation was accompanied by the time-dependent increases in plasma levels of the \*cytokines\* interleukin 12 (IL-12; maximum level reached by 2 hours) and interferon gamma (IFN-gamma; maximum level reached by 18 hours) and was dependent on the oligonucleotide \*CpG\* motif. Ablation of macrophages or NK cells resulted in a loss of in vivo antitumor activity. Conclusion: Immune cell activation, involving the time-dependent activation of macrophages and NK cells, contributes to the antitumor activity of targeted liposome-\*CpG\*-myb-as against neuroblastoma and could improve the effectiveness of antitumor targeted liposomes. (c) Oxford University Press 2004, all rights reserved.

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87.4.1.9 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Antisense nucleotides  
87.4.1.13 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Drug delivery and perfusion  
87.2.8 - \*CANCER\* RESEARCH

7/3,K/2 (Item 2 from file: 71)  
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**Synergistic activation of innate immunity by double-stranded RNA and CpG  
DNA promotes enhanced antitumor activity**

Whitmore M.M.; DeVeer M.J.; Edling A.; Oates R.K.; Simons B.; Lindner D.;  
Williams B.R.G.

ADDRESS: B.R.G. Williams, Department of Cancer Biology, NB40 Lerner  
Research Institute, Cleveland Clinic Foundation, 9500 Euclid  
Avenue, Cleveland, OH 44195, United States

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Double-stranded RNA (dsRNA) and unmethylated \*CpG\* sequences in DNA are pathogen-associated molecular patterns of viruses and bacteria that activate innate immunity. To examine whether dsRNA and \*CpG\* DNA could combine to provide enhanced stimulation of innate immune cells, murine macrophages were stimulated with poly-rI:rC (pIC), a dsRNA analog, and \*CpG\*-containing oligodeoxynucleotides (\*CpG\*-ODN). Combined \*treatments\* demonstrated synergy in nitric oxide, interleukin (IL)-12, \*tumor\* necrosis factor alpha, and IL-6 production. Studies using neutralizing \*antibodies\* for type I interferons (IFNs), IFN-alpha and IFN-beta, indicated that nitric oxide synthase synergism is mediated by paracrine/autocrine effects of IFN-beta. In contrast, enhanced \*cytokine\* production occurred independent of type I IFN and was maintained in macrophages from IFN-alpha/beta receptor knockout mice. Cotransfection of human Toll-like receptors 3 and 9 (receptors for dsRNA and \*CpG\* DNA, respectively) into 293T cells supported synergistic activation of an IL-8 promoter reporter construct by pIC, indicating interaction of the signaling pathways in driving the synergy response. In vivo stimulation of mice with pIC and \*CpG\*-ODN demonstrated synergy for serum IL-6 and IL-12p40 levels that correlated with an enhanced antitumor effect against established B16-FSUB10 experimental pulmonary metastases. \*Treatment\* of \*tumor\*-bearing mice with pIC and \*CpG\*-ODN in combination resulted in enhanced nitric oxide synthase expression in lung tissue and enhanced up-regulation of class I major histocompatibility complex on splenic dendritic cells relative to \*treatments\* with either agent alone. In conclusion, the combined detection of viral pathogen-associated molecular patterns, i.e., dsRNA and \*CpG\* DNA, may mimic definitive viral recognition, resulting in an enhanced innate immune response that could be used for \*tumor\* vaccination or immunotherapy.

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...\*TREATMENT\* / ...

...Chemotherapy

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...\*TREATMENT\* / \*Treatment\* Monitoring and Evaluation

### 86.9.3 - IMMUNOLOGY AND INFECTIOUS DISEASES

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#### CEL-1000 - A peptide with adjuvant activity for Th1 immune responses

Charoenvit Y.; Goel N.; Whelan M.; Rosenthal K.S.; Zimmerman D.H.

ADDRESS: D.H. Zimmerman, CEL-SCI Corporation, Vienna VA, 8229 Boone Blvd,  
Vienna, VA 22182, United States

EMAIL: dzimmerman@cel-sci.com

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...1000 (derG, DGQEEKAGVVSTGLIGGG) is a small immunomodulatory peptide which delivers demonstrated protective activity in two infectious disease challenge models (HSV and malaria) and an allogenic \*tumor\* vaccine model. CEL-1000 and other activators (defensin-beta, \*CpG\* ODN, and imiquimod) of the innate immune system promote IFN-gamma-associated protective responses. CEL-1000 is an improved form of peptide G (a peptide from human MHC II beta chain second domain, aa 135-149) known to enhance immune responses of other immunogenic peptides. Since defensin-beta, \*CpG\* ODN, and imiquimod have been shown to possess adjuvant activity, we investigated the adjuvant effect of peptide G and CEL-1000 as conjugates with HIV and malaria peptides. \*Antibody\* titers and isotypes were evaluated on serum taken from select days following immunization. Results for CEL-1000 and G peptide conjugates were compared with results...

...either G or KLH-HGP-30 peptide conjugates. In another study, CEL-1000 conjugates (CEL-1000-HGP-30) demonstrated a 4-10-fold higher titer \*antibody\* response than seen with several other peptide conjugates of the same HGP-30 peptide. Improved adjuvant activity of CEL-1000 in peptide conjugates was also demonstrated by a shift in the \*antibody\* isotypes toward a Th1 response (IgG2a). The IgG2a/IgG1, ratio for G-HGP-30 HIV or KLH-HGP-30 HIV conjugates were lower than for...

...a malaria peptide conjugate (CEL-1000-SF/GF) compared to the un-conjugated peptide (SF-GF). CEL-1000 also showed adjuvant activity in an allogenic \*tumor\* vaccine model. As expected for an adjuvant, CEL-1000 or G does not induce detectable self-directed or cross reactive \*antibodies\*. CEL-1000 is currently being investigated for use as an adjuvant with conventional vaccines. It is expected that IgG2a \*antibodies\* would be preferably generated by CEL-1000 adjuvancy and could enhance in vivo clearance of antigens or pathogens. (c) 2004 Elsevier Ltd. All rights reserved.

#### DESCRIPTORS:

CEL-1000; \*Cytokines\*; IgG2a \*antibodies\*; Gamma interferon

#### CLASSIFICATION CODE AND DESCRIPTION:

...Active specific

87.4.3.2 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Active specific

87.2.11.3 - \*CANCER\* RESEARCH

7/3,K/4 (Item 4 from file: 71)

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**Whole cell ELISA for measuring anti-tumour effects of immunotherapies in a mouse tumour model of ALCL**

Carstens M.; Bittner C.; Krokowski M.; Hadlak M.; Feller A.C.; Merz H.

ADDRESS: M. Carstens, St. Annen-Str. 16, D-23552 Lubeck, Germany

EMAIL: m.carstens@gmx.de

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SUMMARY LANGUAGES: English

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...explored throughout the last century. Using the recently established TS1G6 ALCL mouse model, we compared the ability of whole cell vaccines with different combinations of \*CpG\* oligodeoxynucleotides, Diphteria-, Pertussis- and Tetanus-vaccine (DPT) to enhance the immunogenicity of tumour cells. We have therefore developed a whole cell ELISA that detects the systemic anti-\*tumor\*-cell \*antibody\* response. \*CpG\* oligodeoxy-nucleotides can induce production of different TH1-\*cytokines\* and stimulate immune effector cells. Diphteria-, Pertussis- and Tetanus-vaccine, injected together with irradiated \*tumor\* cells into Diphteria-, Pertussis- and Tetanus-preimmunized mice were used to serve as a target for the host's existing memory response and thus enhance the immunogenicity of the tumour cells by induction of a local inflammation. The combined application of oligodeoxynucleotides, the vaccines and irradiated \*tumor\* cells into preimmunized mice quickly induced very high titers of tumour cell-specific \*antibody\* response. We conclude that this therapy may be a new attractive part of a tumour immunization strategy.

CLASSIFICATION CODE AND DESCRIPTION:

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immunotherapy

87.2.8 - \*CANCER\* RESEARCH

7/3,K/5 (Item 5 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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**\*CpG\* oligonucleotides enhance the \*tumor\* antigen-specific immune response of a granulocyte macrophage colony-stimulating factor-based vaccine strategy in neuroblastoma**

Sandler A.D.; Chihara H.; Kobayashi G.; Zhu X.; Miller M.A.; Scott D.L.; Krieg A.M.

ADDRESS: A.D. Sandler, Division of Pediatric Surgery, University of Iowa,  
200 Hawkins Drive, Iowa City, IA 52242, United States

EMAIL: anthony-sandler@uiowa.edu

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NO. OF REFERENCES: 37

**\*CpG\* oligonucleotides enhance the \*tumor\* antigen-specific immune response  
of a granulocyte macrophage colony-stimulating factor-based vaccine  
strategy in neuroblastoma**

Granulocyte macrophage colony-stimulating factor (GM-CSF)-transduced autologous \*tumor\* cells form the basis of many immunotherapeutic strategies. We tested whether combining this approach with T-helper 1 (Th-1)-like immunostimulatory \*CpG\* oligodeoxynucleotides (\*CpG\* ODNs) would improve therapeutic efficacy in an established model of murine neuroblastoma. The weakly immunogenic Neuro-2a cell line was used in syngeneic A/J mice. \*CpG\* 1826 was tested for its antitumor effect alone and as an adjuvant to Neuro-2a cells retrovirally transduced to express murine GM-CSF (GM/Neuro-2a). Three days after wild-type (WT) \*tumor\* cell inoculation, mice in different groups were s.c. vaccinated in the opposite leg with combinations of WT neuro2a, irradiated (15 Gy) WT or GM/Neuro-2a transfectants with or without \*CpG\* 1826 (200 mug). To test for the induction of memory responses, mice that rejected their \*tumor\* were rechallenged with WT Neuro-2a (1 x 10<sup>5</sup> SUP6) 7 weeks after vaccination. All of the mice in the control (unvaccinated) group died within 3 weeks after Neuro-2a inoculation. Most of the vaccinated groups had only minimal-to-modest antitumor responses, and the mice succumbed to \*tumor\*. \*Tumor\* growth was remarkably inhibited in the group of mice that received irradiated GM/Neuro-2a plus \*CpG\* and four (50%) of eight mice in this group survived \*tumor\* free. \*Tumor\*-free mice were resistant to further WT \*tumor\* cell challenge, indicating a memory response. Mechanistic studies showed that \*CpG\* alone induced a favorable Th-1-like \*cytokine\* immune response and vaccine-induced \*tumor\* cell killing was dependent on both CD4 and CD8 T cells that killed \*tumor\* cell targets by apoptosis. These results demonstrate that \*CpG\* ODNs enhanced the antitumor effect of irradiated GM-CSF secreting Neuro-2a cells. This vaccine strategy elicits a potent \*tumor\* antigen-specific immune response against established murine neuroblastoma and generates systemic neuroblastoma-specific immunity.

CLASSIFICATION CODE AND DESCRIPTION:

87.2.11.1 - \*CANCER\* RESEARCH...

...Tumour antigens

87.2.11.4 - \*CANCER\* RESEARCH...

...Immune response - \*antibody\*-directed responses

87.4.3.4 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immune response - \*antibody\*-directed responses



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**Comparison of the effect of different immunological adjuvants on the  
\*antibody\* and T-cell response to immunization with MUC1-KLH and GD3-KLH  
conjugate \*cancer\* vaccines**

Soo Kie Kim; Ragupathi G.; Musselli C.; Choi S.-J.; Yoon Sun Park;  
Livingston P.O.

ADDRESS: P.O. Livingston, Lab. of Devmtl. Tumor Vaccinology, Memorial  
Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021  
, United States

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**Comparison of the effect of different immunological adjuvants on the  
\*antibody\* and T-cell response to immunization with MUC1-KLH and GD3-KLH  
conjugate \*cancer\* vaccines**

While the importance of immunological adjuvants for optimal induction of \*antibody\* and T-cell responses against \*tumor\* antigens is clear, the relevant potency of different adjuvants is not clear. We have screened 19 different immunological adjuvants with KLH conjugate vaccines containing the two human \*cancer\* antigens (MUC1 peptide and GD3 ganglioside) in the mouse. ELISA assays for IgM and IgG \*antibody\* responses as well as proliferation and \*cytokine\* release (IFN-gamma and IL-4) for T-cell responses were performed. Six adjuvants stood out as being especially effective for induction of IgM and IgG \*antibodies\* against both MUC1 and GD3: QS-21, TiterMax, MoGM-CSF, MPL/DETOX and \*CpG\* ODN. Of these QS-21, MPL/DETOX and MoGM-CSF were uniformly effective at inducing potent proliferation and potent IFN-gamma and IL-4 responses against KLH while TiterMax and \*CpG\* ODN generated potent IFN-gamma responses but less potent proliferation or IL-4 release. Overall, as in our previous experience, QS-21 was the most...

...clear evidence for induction of T-cell immunity against either GD3 or MUC1 with any of the adjuvants. There was a strong correlation between the \*antibodies\* induced against MUC1 and GD3 with different immunological adjuvants and the strength of the IFN-gamma release against KLH. This suggests that the primary role...

...in the context of these conjugate vaccines may be induction of higher levels of T-cell immunity against KLH, which then leads to higher levels \*antibody\* against the conjugated antigens.

**CLASSIFICATION CODE AND DESCRIPTION:**

...Tumour Immunotherapy

87.3.1 - \*CANCER\* RESEARCH...

...Classification and Prognostic Indicators

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / ...

...Immunotherapy

87.4.11 - \*CANCER\* RESEARCH...

...\*TREATMENT\* / \*Treatment\* Monitoring and Evaluation

7/3,K/7 (Item 7 from file: 71)

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**Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif are effective as immune adjuvants in \*tumor\* antigen immunization**

Weiner G.J.; Liu H.-M.; Wooldridge J.E.; Dahle C.E.; Krieg A.M.

ADDRESS: G.J. Weiner, C32 General Hospital, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, United States

EMAIL: george-weiner@uiowa.edu

Journal: Proceedings of the National Academy of Sciences of the United States of America, 94/20 (10833-10837), 1997, United States

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**Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif are effective as immune adjuvants in \*tumor\* antigen immunization**

Recent advances in our understanding of the immune response are allowing for the logical design of new approaches to \*cancer\* immunization. One area of interest is the development of new immune adjuvants. Immunostimulatory oligodeoxynucleotides containing the \*CpG\* motif (\*CpG\* ODN) can induce production of a wide variety of \*cytokines\* and activate B cells, monocytes, dendritic cells, and NK cells. Using the 38C13 B cell lymphoma model, we assessed whether \*CpG\* ODN can function as immune adjuvants in \*tumor\* antigen immunization. The idiotype served as the \*tumor\* antigen. Select \*CpG\* ODN were as effective as complete Freund's adjuvant at inducing an antigen-specific \*antibody\* response but were associated with less toxicity. These \*CpG\* ODN induced a higher titer of antigen-specific IgG2a than did complete Freund's adjuvant, suggesting an enhanced TH1 response. Mice immunized with \*CpG\* ODN as an adjuvant were protected from \*tumor\* challenge to a degree similar to that seen in mice immunized with complete Freund's adjuvant. We conclude that \*CpG\* ODN are effective as immune adjuvants and are attractive as part of a \*tumor\* immunization strategy.

CLASSIFICATION CODE AND DESCRIPTION:

87.2.11 - \*CANCER\* RESEARCH...

...Immunology

87.4.3 - \*CANCER\* RESEARCH...

...\*TREATMENT\* /

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**Molecular pathogenesis of lung \*cancer\*.**

Zochbauer-Muller, Sabine

Gazdar, Adi F; Minna, John D

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**Molecular pathogenesis of lung \*cancer\*.**

**ABSTRACT:** Lung \*cancer\* is the most common cause of \*cancer\* death in the United States, killing more than 156,000 people every year. In the past two decades, significant progress has been made in understanding the molecular and cellular pathogenesis of lung \*cancer\*. Abnormalities of proto-oncogenes, genetic and epigenetic changes of \*tumor\* suppressor genes, the role of angiogenesis in the multistage development of lung \*cancer\*, as well as detection of molecular abnormalities in preinvasive respiratory lesions, have recently come into focus. Efforts are ongoing to translate these findings into new clinical strategies for risk assessment, chemoprevention, early diagnosis, \*treatment\* selection, and prognosis and to provide new targets and methods of \*treatment\* for lung \*cancer\* patients. All these strategies should aid in reducing the number of newly diagnosed lung \*cancer\* cases and in increasing the survival and quality of life of patients with lung \*cancer\*. Reprinted by permission of the publisher.

**TEXT:**

Key Words \*tumor\* suppressor gene, allele loss, methylation, angiogenesis, preneoplasia

1 Abbreviations: NSCLC, non-small cell lung \*cancer\*; SCLC, small cell lung \*cancer\*; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; NMB, neuromedin B; NMBR, neuromedin B receptor; BRS-3, bombesin receptor subtype 3; IGF, insulin-like growth factor; PDGR, platelet-derived growth factor; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; TSG, \*tumor\* suppressor gene; LOH, loss of heterozygosity; FHIT gene, fragile histidine triad gene; RARb, retinoic acid receptor b; p14, p14ARF; RB, retinoblastoma gene; CDK, cyclin-dependent...  
...death-associated protein kinase; ECAD, E-cadherin; GSTP1, glutathione-S-transferase P1; p15, p15INK4b; VEGF, vascular epithelial growth factor; RER, replication error repair

**INTRODUCTION**

Lung \*cancer\* is one of the most prevalent and lethal cancers in the world. In the United States about 156,000 people died because of lung \*cancer\* last year, which represents 28[percent] of all \*cancer\* deaths (1). Although the rate of lung \*cancer\* deaths for males is decreasing in the United States, the mortality associated with lung \*cancer\* among women continues to increase (2). Cigarette smoking is the main risk factor for lung \*cancer\*, accounting for about 90[percent] of the cases in men and 70[percent] of the cases in women (3, 4). Exposures to other environmental and occupational respiratory carcinogens may be interactive with cigarette smoking and thus also influence lung \*cancer\* incidence. Nevertheless, prevention of smoking initiation and increased smoking cessation remain the best long-term methods to prevent lung \*cancer\* development. The major histologic types of lung \*cancer\* are non-small cell lung cancers

(NSCLC), (FN1) which represent about 80[percent] of lung cancers and are divided into squamous cell carcinoma, adenocarcinoma (including...

...cell carcinoma and mixed types, and small cell lung cancers (SCLC), which represent about 20[percent] of lung cancers. Development of metastases when the primary \*tumors\* are still small, coupled with lack of methods for early diagnosis and of systemic therapies with great efficacy to deal with micrometastatic disease are the main reasons why the prognosis of lung \*cancer\* patients is still poor, with over-all 5-year survival rates of about 14[percent] (5). Thus new methods for early detection and identification of smokers at greatest risk for developing lung \*cancer\*, such as spiral-computed tomography screening for early lung cancers, biomarkers for lung \*cancer\* risk assessment, new approaches for lung \*cancer\* prevention (chemo-prevention), and new drugs based on rational targets, are necessary and need to be developed. In this review we summarize the advances that have been made in understanding the molecular and cellular biology of lung \*cancer\* over the recent years (major molecular abnormalities summarized in Table 1). It is hoped that these new findings will result in novel approaches for prevention and early detection of lung \*cancer\* and new effective \*treatment\* strategies for lung \*cancer\* patients.

AUTOCRINE AND PARACRINE SYSTEMS: GROWTH FACTORS AND THEIR RECEPTORS  
Many growth factors and their receptors are expressed by lung \*cancer\* cells or adjacent normal cells leading to the development of several autocrine or paracrine growth stimulatory loops (6). One of the best-characterized autocrine systems...

...in NSCLCs, whereas the expression of GRPR and BRS-3 is less frequent (9). Also the ligands for these receptors are often expressed in lung \*cancer\* cells leading to potential self-stimulatory (autocrine) loops. The NMB gene is expressed in 100[percent] of SCLCs and NSCLCs (10). Approximately 20-60[percent]...

...two expressed copies of the X-linked GRPR gene in females may be a factor in the increased susceptibility of women to tobacco-induced lung \*cancer\*. Blocking this system with \*antibodies\* or receptor antagonists results in inhibition of \*tumor\* growth in model systems; this concept is being explored as a new therapeutic avenue (13). Other peptides with potential autocrine growth function in lung \*cancer\* are insulin-like growth factors (IGF) I and II (14). Wu et al. (15) tested the hypothesis that accumulation of genetic damage is dependent on...

...blood levels of IGF-I and the molar ratio of IGF-I/IGF-binding protein-3 were higher in patients with advanced or poorly differentiated \*cancer\* than in patients with early or well-differentiated cancers.

The c-erbB-1 proto-oncogene encodes the receptor for the epidermal growth factor (EGFR), which regulates epithelial proliferation and differentiation and is activated in lung \*cancer\* cells by overexpression (16, 17). The EGFR gene was found to be overexpressed in 13[percent] of NSCLCs (18), and EGFR protein expression by \*tumors\* seems to be a poor prognosis risk factor in NSCLC patients (...185 kDa (p 185neu), is another growth factor receptor and is frequently expressed in NSCLCs, but not in SCLCs (20, 21). Using an anti-p185HER2 \*antibody\*, inhibition of human lung \*cancer\* cell line growth has been demonstrated (22), whereas anti-EGFR \*antibodies\* can inhibit the growth of human \*tumor\* cell lines overexpressing EGFR. The use of humanized monoclonal anti-HER2 \*antibody\* (Herceptin) has been tested in breast \*cancer\* \*treatment\* with promising results and is also being evaluated clinically in lung \*cancer\*.

Additionally, several new drugs have been developed that block the tyrosine kinase activity of these receptors, which leads to \*tumor\* growth inhibition in preclinical models; these drugs have also recently gone into clinical trials.

The hepatocyte growth factor (HGF) and its receptor comprise another growth factor/receptor complex that may play a role in lung \*cancer\* development. HGF, which stimulates epithelial cells to proliferate, move, and carry out differentiation programs, is expressed in many NSCLCs (23, 24) where it is associated...

...The receptor for HGF is encoded by the oncogene MET, which is expressed in normal lung epithelium, SCLCs, and NSCLCs (23, 24, 26). Thus these \*tumor\* cells have both the receptor and the ligand for this growth factor.

Data in the literature concerning the expression of estrogen and progesterone receptors in human lung \*cancer\* are discordant. Di Nunno et al. (27) did not find estrogen or progesterone receptor expression in a large series of NSCLC samples, whereas Su et...

...by p53. Forced overexpression of oncogenic MYC or RAS in fibroblasts can lead to apoptosis in the face of nutrient deprivation. It is likely that \*tumor\* cells over-express BCL-2 to overcome apoptotic signals from MYC and RAS expression. Immunohistochemical studies have shown that BCL-2 protein is expressed frequently...

...expression is higher in squamous cell carcinomas than in adenocarcinomas (37). Of interest, some studies demonstrate a survival benefit for patients with BCL-2-positive \*tumors\* (37-40) while others do not confirm this finding (41). A higher response rate to chemotherapy was observed for BCL-2-positive \*tumors\* compared with BCL-2-negative \*tumors\*, suggesting that BCL-2 expression reflects a higher susceptibility to cytotoxic \*treatment\* (38). Antisense BCL-2 drugs, which block translation of BCL-2 protein in \*tumor\* cells, will soon be tested in clinical trials. These drugs may work either alone or by increasing a \*tumor\* cell response to standard chemotherapy and radiotherapy.

#### NOTCH-3

Notch-3 is located on chromosome 19p in a region that was found to be translocated...

...associated with chromosome 19p translocation (42). This finding is of particular interest because it demonstrates that a specific chromosome translocation occurs in a common epithelial \*cancer\* and activates a gene not previously implicated in lung \*cancer\*.

#### AIS

AIS (amplified in squamous cell carcinoma) is a p53 homologue located on the distal long arm of chromosome 3 with multiple protein products (p40...

...analysis revealed frequent amplification of this gene locus in primary lung squamous cell carcinomas, and protein overexpression was observed in lung squamous cell carcinomas and \*tumors\* known to harbor a high frequency of p53 mutations, suggesting that AIS plays an oncogenic role in lung squamous cell carcinomas (43). Circulating anti-p40 (AIS) \*antibodies\* have been detected in the sera of respiratory tract \*cancer\* patients, but the presence or absence of AIS \*antibodies\* were independent of other clinicopathological characteristics of these patients (44).

#### CHROMOSOMAL SITS OF FREQUENT ALLELE LOSS AND \*TUMOR\* SUPPRESSOR GENES

(TSGS)

According to Knudson's two-hit hypothesis (45), loss of function of TSGs requires that both alleles have to be inactivated. One...

...region referred to as allele loss or loss of heterozygosity (LOH) (30, 46). Thus consistent LOH for genetic markers at a given locus in many \*tumors\* is strong evidence for the presence of one or more TSGs in that region. Recently, a genome-wide high-resolution search of LOH was performed ...

...carcinomas and primary adenocarcinomas was also investigated in the study by Wistuba et al. (48) using 19 polymorphic microsatellite markers at 12 chromosomal regions. Each \*tumor\* type had a characteristic pattern of allelic loss, and the bronchial epithelium accompanying SCLCs showed a much higher frequency of LOH compared with squamous cell...

...by Sanchez-Cespedes et al. (49) reported a much higher frequency of widespread chromosomal abnormalities in lung adenocarcinomas from smokers compared with infrequent changes in \*tumors\* arising in nonsmokers.

So far, 3p allele loss has been shown to be the most frequent molecular alteration in lung cancers (47, 50, 51). However, 3p allele loss occurs not only in \*tumors\* but also in the normal epithelium of smokers without lung \*cancer\*, and hyperplasias, dysplasias, and carcinoma in situ in the respiratory epithelium accompanying lung cancers, suggesting that it is an early change in the multistep pathogenesis of lung \*cancer\* (51-53). A high-resolution 3p LOH study in primary lung \*tumors\* and preneoplastic/preinvasive lesions using a panel of 28 microsatellite markers demonstrated a progressive increase in the frequency and size of 3p allelic loss regions...

...transcripts that are produced by alternative promoter selection and alternative mRNA splicing. mRNA expression of one of these transcripts, RASSF1A, is frequently lost in lung \*cancer\*. The major mechanism for inactivating RASSF1A is by aberrant methylation of its promoter region turning off its expression; inactivation of RASSF1A by mutation is rare (56-58). Additionally, the study by Burbee et al. (57) shows that patients whose \*tumors\* are methylated for RASSF1A have a shorter overall survival rate than patients whose \*tumors\* are not methylated for RASSF1A. Thus these data strongly support the candidacy of RASSF1A as a TSG that plays a major role in the pathogenesis of lung \*cancer\*. The FHIT (fragile histidine triad) gene, a candidate TSG that spans the FRA3B common fragile site at 3p14.2, was found to be frequently abnormal in lung \*cancer\* (59, 60). Aberrant FHIT transcripts were detected in 80[percent] of SCLC and 40[percent] of NSCLC specimens (59, 60), and absent FHIT protein expression ...

...more frequently in smokers than in nonsmokers, suggesting that FHIT is a molecular target of tobacco smoke carcinogens (61). Recently, aberrant methylation of the 5' \*CpG\* island of the FHIT gene was shown to be an important mechanism for silencing this gene in lung \*cancer\* (63). Transfection of a wild-type copy of FHIT into lung \*cancer\* cells can reverse the malignant phenotype and induce \*tumor\* cell apoptosis (64, 65); this suggests that FHIT overexpression could serve as a future therapeutic approach.

The retinoic acid receptor  $\beta$ -2 (RAR $\beta$ ) gene located at 3p24 has been intensively studied in lung \*cancer\* and found to have defective function, thus making it a candidate TSG. This is particularly important given the interest in using retinoids as chemoprevention agents for lung \*cancer\*. RAR $\beta$  is a key retinoid receptor that mediates growth control responses, and considerable evidence suggests that RAR $\beta$  abnormalities exist in lung

cancers (66-69). A lung \*cancer\* cell line Calu-1 (70). Frequent loss of RARb mRNA expression has been described in both primary NSCLCs and bronchial biopsy specimens from heavy smokers...

...screening for homozygous deletions, a homozygously deleted region on chromosome 2q has been identified (84). This region harbors the lipoprotein receptor-related protein-deleted in \*tumors\* (LRP-DIT) gene. Homozygous deletions in LRP-DIT were detected in 17[percent] of NSCLC cell lines, and expression of only abnormal transcripts missing parts...

...Recently, the TSLC1 gene has been identified at chromosome 11q23.2 (85). This region is of particular interest because LOH occurs frequently and, in addition, \*tumorigenicity\* of A549 lung \*cancer\* cells can be suppressed by this region. Moreover, loss of TSLC1 expression was observed frequently in NSCLCs, and aberrant methylation of the promoter region has...

...isoform of the A subunit of the serine/threonine protein phosphatase 2A (PP2A), was found to be altered by mutations in lung, colon, and breast \*cancer\*, thus suggesting it as a putative TSG (86).

### P53

The p53 gene, located at chromosome region 17p13.1, encodes a 53-kDa nuclear protein. This...

...genes results in apoptosis, cell cycle arrest, and DNA repair. Mutations of the p53 gene comprise some of the most common genetic changes associated with \*cancer\* and cause loss of \*tumor\* suppressor function and loss of ability to induce apoptosis. The prevalent type of point mutations is a GC to TA transversion causing missense mutations. This...

...in protein studies, and the incidence of p53 overexpression and mutations in adenocarcinomas was significantly lower than that in squamous cell carcinomas.

As a new \*treatment\* approach, p53 has been introduced into clinical trials with retroviral and adenoviral gene therapy delivered directly into \*tumors\* with initially promising antitumor responses (100). A recent study investigated the additional benefit from adenoviral p53 gene therapy directly injected into \*tumors\* in patients undergoing first-line chemotherapy for NSCLC (101). However, no differences in response rates or survival were observed between the group \*treated\* with additional p53 gene therapy and the group \*treated\* with chemotherapy alone. The successful systemic delivery of p53 by liposomes has been shown recently in lung \*cancer\* (102) and needs to be investigated further for \*treatment\* of primary and disseminated lung \*cancer\*. In addition, vaccine trials using mutant p53 peptides have been completed (103).

### THE P16INK4-CYCLIN D1-CDK4-RB PATHWAY

p16INK4 (p16) was mapped to the...binding to the MDM2-p53 complex, it prevents p53 degradation, thereby leading to p53 activation. Loss of p14 expression was more frequently found in lung \*tumors\* with neuroendocrine features (110). However, aberrant methylation of the p14 promoter region did not occur frequently in NSCLCs (108).

The other key component in this...

...which is found in [similar]90[percent] of all lung cancers. However, it is uncommon to have both RB and p16 inactivated in the same \*tumor\*. Loss of RB function can occur by deletions, mutations, or splicing abnormalities. Abnormalities of the RB protein are found in more than 90[percent] of...

...grading and development of metastasis in lung cancers (118). Recently, Claudio et al. (119) reported a high frequency of RB2/p130 mutations in primary lung \*tumors\*. Retrovirus-mediated delivery of wild-type RB2/p130 to a lung \*tumor\* cell line potentially inhibited \*tumorigenesis\*, suggesting that RB2/p130 may be a candidate for gene therapy trials for lung \*cancer\*.

#### APC (ADENOMATOUS POLYPOSIS COLI) GENE/WNT PATHWAY

The APC gene encodes a large protein with multiple cellular functions and interactions, including roles in signal transduction...

...APC has been frequently observed in primary lung cancers, and aberrant methylation is the most important mechanism for inactivating expression of this gene in lung \*cancer\* (121). With loss of APC expression, the wnt-signaling pathway is constitutively turned on, resulting in accumulation of b-catenin as the result of wnt...

...and cyclin D1, both of which regulate cell cycle progression. Although this could also occur by b-catenin mutations, these mutations are rare in lung \*cancer\*.

The occurrence of mutations in the PTEN/MMAC1 gene, which is located at the chromosomal region 10q23.3, has been investigated in a large number ...

...that genetic abnormalities of this gene are only involved in a relatively small subset of lung cancers.

#### ABERRANT PROMOTER METHYLATION

Aberrant methylation of normally unmethylated \*CpG\*-rich areas, also known as \*CpG\* islands that are located in or near the promoter region of many genes, has been associated with transcriptional inactivation of TSGs in human \*cancer\* (105, 123). Methylation serves as an alternative to the genetic loss of a TSG function by deletion or mutation. As discussed above, several genes are frequently methylated in primary lung \*tumors\* including the genes adenomatous polyposis coli (APC), retinoic acid receptor b-2 (RARb), CDH13 (H-cadherin), fragile histidine triad (FHIT), RASSF1A, tissue inhibitor of metalloproteinase...

...death-associated protein kinase (DAPK) (56-58, 63, 74, 105, 108, 121, 124-128) (Table 2). A significantly shorter disease-free survival for patients whose \*tumors\* were methylated for DAPK was reported by Tang et al. (128), and Burbee et al. (57) found a shorter overall survival for patients whose tumors were methylated for RASSF1A. Methylated DNA sequences can be detected in primary lung cancers, circulating in serum DNA from lung \*cancer\* patients, in sputum samples prior to the onset of invasive lung \*cancer\*, as well as in precursor lesions for lung carcinomas (106, 129, 130). These findings indicate that aberrant methylation can develop during the preneoplastic process and thus may serve as a potential biomarker for early diagnosis of lung \*cancer\*, as well as in following disease load. Determining the methylation status of certain genes in bronchial biopsies, bronchioloalveolar washings, and sputum samples from high-risk individuals such as heavy smokers is being tested as a marker for lung \*cancer\* risk assessment. Aberrant methylation can be reversed in vitro by drugs that block methylation such as 5-aza-2'-deoxycytidine, which results in gene re-expression and \*tumor\* growth inhibition (63, 74). Histone deacetylase inhibitors also can reverse the methylation status of genes and frequently are additive or synergistic with 5-aza-2'-deoxycytidine. Because of the frequency of \*tumor\*-acquired methylation, clinical trials with demethylating drugs such as 5-aza-2'-deoxycytidine, with or without histone deacetylase inhibitors, are being developed (131).



#### \*TUMOR\* ANGIOGENESIS

Angiogenesis is important in neoplastic development and progression because both \*tumor\* growth and metastatic dissemination of \*tumor\* cells depend on vascular support (132). An increasing number of angiogenic factors, i.e., inducers and inhibitors regulating endothelial cell proliferation and migration, have been identified (132-134). Angiogenic factors affect vasculature formation, growth patterns, and vascular permeability, modulate host response, and influence \*tumor\* invasion, metastasis, and prognosis. \*Tumor\* cells and their precursor cells are able to secrete angiogenic substances that depend on certain factors including hypoxia and alterations in dominant and recessive oncogenes...

...prime regulators of both physiological and pathological angiogenesis (134). So far, two receptors for VEGF, which are selectively expressed in endothelium, have been characterized, and \*antibodies\* have been developed that can block the interaction between VEGF and its ...139). This fact is important because dendritic cells are important for antigen presentation and suggest that inadequate function may be responsible for the escape of \*tumors\* from the host immune system. VEGF expression in NSCLCs was significantly associated with new vessel formation and was an adverse prognostic factor in these patients (140). Koukourakis et al. (141) investigated the activated microvessel density in early operable NSCLCs and found it significantly higher in the invading front of the \*tumors\* and in the normal lung adjacent to the \*tumors\* compared with normal lung distal to the \*tumor\* or the inner \*tumor\* areas. These results suggest that activated microvessel density serves as an independent prognostic factor in NSCLC patients. Upregulation of platelet-derived endothelial cell growth factor...

...the microvessel count was a highly significant adverse predictor of both overall and disease-free survival in patients with NSCLC, suggesting that the evaluation of \*tumor\* angiogenesis may be useful in the postsurgical staging of NSCLC patients to identify subsets of patients who may benefit from adjuvant \*treatment\* studies. New \*treatment\* approaches directed against angiogenic factors or their receptors are being investigated in clinical trials in lung \*cancer\*. These include humanized monoclonal anti-VEGF \*antibodies\*, anti-VEGF receptor \*antibodies\*, and drugs blocking the VEGF receptors' tyrosine kinase activity essential for their function.

#### TOBACCO SMOKE CARCINOGENS

Tobacco smoke is responsible for about 90[percent] of all cases of lung \*cancer\*. The three major classes of carcinogens in tobacco smoke are the polycyclic hydrocarbons such as benzo(a)pyrene, nitrosamines, and aromatic amines (144). The carcinogenic...

...which may result in DNA misreplication and mutation. A significant association between the level of benzo(a)pyrene-induced DNA adducts and risk for lung \*cancer\* has been reported and suggests that subjects sensitive to benzo(a)pyrene-induced DNA damage may have a suboptimal ability to remove benzo(a)pyrene-DNA adducts. These subjects are thus susceptible to tobacco carcinogen exposure and may be at increased risk of developing lung \*cancer\* (145).

#### ALTERATIONS IN SMOKE-DAMAGED RESPIRATORY EPITHELIUM

Lung cancers are believed to arise after a series of progressive pathological changes in the respiratory epithelium, and...

...areas of dysplasia and in atypical alveolar hyperplasia (147). LOH at chromosomal regions 8p and 9p occurs early in the multistage development of invasive lung \*cancer\*; however, LOH at 3p is the earliest and most frequent event (51, 52, 148, 149). Allele loss at 8p21-23, commenced at the hyperplasia/metaplasia stage, was seen in 65[percent] of smokers without \*cancer\* and persisted for up to 48 years after smoking cessation. Similar to LOH found at chromosome 3p, there was also a progressive increase in the ...

...size of allele loss with increasing severity of histopathologic preneoplastic changes. LOH was also detected in plasma DNA from individuals at high risk of lung \*cancer\* (150). Recently, aberrant methylation of certain genes has been linked to early stages of respiratory carcinogenesis. Belinsky et al. (129) reported that aberrant methylation of ...

...of neoplasia (151), and p16 methylation, p53 mutations, KRAS mutations, and microsatellite instability were detected in bronchoalveolar lavage fluid from patients with early-stage lung \*cancer\* (152). Additionally, aberrant methylation of FHIT has been found in the smoking-damaged bronchial epithelium from heavy smokers without \*cancer\* (63). A high frequency of mitochondrial DNA (mtDNA) mutations have been described in various malignant \*tumors\* including lung \*cancer\* (153). The mutated mtDNA was detectable in bronchoalveolar lavage fluids, suggesting that it may serve as a powerful molecular marker for detection of lung \*cancer\*. The functional significance of such mitochondrial changes is currently unknown.

The fact that specific alterations can be detected in preneoplastic/preinvasive lesions suggests that these abnormalities may be useful as biomarkers for lung \*cancer\*. These biomarkers could be used to identify individuals at high risk for developing lung \*cancer\*, monitor the efficacy of lung \*cancer\* chemoprevention trials, diagnose lung \*cancer\* in early stages, and monitor the efficacy of lung \*cancer\* therapies. Additionally, study of biomarkers in \*tumors\* could identify patients with different prognoses and allow tailoring of therapy. Samples used to test for biomarkers for risk assessment have to be obtainable in...

...in about 35[percent] of SCLCs and 22[percent] of NSCLCs (30). Thus microsatellite alterations have been tested as molecular biomarkers for early detection of \*cancer\* cells in sputum and bronchial washings (152, 154). In other human \*tumors\* such as colon \*cancer\*, the replication error repair (RER) phenotype results in "laddering" of short tandem repeat sequences associated with inherited or acquired mutations in DNA mismatch repair genes such as MSH2 and hMLH1 (30). However, this RER phenotype or mutations in these genes have not been found in lung cancers. Lung \*tumors\* with microsatellite alterations at selected tetranucleotide repeats have a high frequency of p53 mutations and do not display a phenotype consistent with defects in mismatch repair (155). The molecular abnormalities underlying such microsatellite alterations in lung \*cancer\* are unknown.

#### TELOMERASE ACTIVITY

The ends of human chromosomes (telomeres) contain the hexameric TTAGGG tandem repeats. During normal cell division, the absence of telomerase activity is associated with progressive telomere shortening, leading to cell senescence and normal cell mortality (30). On the contrary, germ cells, some stem cells, and most \*cancer\* cells have telomerase activity that results in replacing the hexameric repeats, therefore leading to potential cellular immortality (30). The majority of SCLCs and about 80... and advanced stage in NSCLCs (157). Because of this, anti-telomerase drugs are being developed as new therapeutics for a variety of cancers

including lung \*cancer\*. Telomerase components are activated in the latent preneoplastic stages of lung \*cancer\*. The mechanism for re-expression of the catalytic component hTERT or the RNA component of telomerase in \*tumors\* is currently unknown. Normal epithelial cells can be immortalized and transformed to malignancy by the combination of hTERT, SV40 T antigen, and a mutated RAS gene (158).

#### NEUROENDOCRINE PHENOTYPE OF LUNG \*TUMORS\*

The classification of neuroendocrine (NE) lung \*tumors\* includes carcinoids and SCLCs and has been enlarged with a new entity, the large cell NE carcinomas (LCNEC) (159). NE lung \*tumors\* share certain morphological, ultrastructural, immunohistochemical, and other molecular characteristics that sustain their NE phenotype (e.g., NE secretory granules at electron microscopy, NE markers at immunohistochemistry) (159). Specific NE markers include chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM). NE lung \*tumors\* appear to be epithelial \*tumors\* characterized by their preferential NE differentiation but retain their propensity to follow multidirectional differentiation pathway. The derivation of all histologic types of lung \*cancer\* from a common endodermal stem cell is likely to be responsible for the frequent multidirectional differentiation in lung \*tumors\*. However, this stem cell has not yet been identified.

#### VIRAL FACTORS IN THE PATHOGENESIS OF LUNG \*CANCER\*

There is no evidence yet that HIV infection leads to an increased incidence of lung \*cancer\*. However, lung \*tumors\* arising in HIV-positive patients with or without the acquired immunodeficiency syndrome (AIDS) have a severalfold increase in the frequency of microsatellite alterations, which indicates increased genetic instability (160).

Lung \*cancer\* is the leading cause of \*cancer\* death in Taiwanese women, although less than 10[percent] of female lung \*cancer\* patients are smokers, which suggests that other factors are important for developing lung \*cancer\* (161). A recent study indicated that human papillomavirus (HPV) oncogenic subtypes 16/18 may be involved in the pathogenesis of lung \*cancer\* of these Taiwanese women (161). Fifty-five percent of lung \*tumor\* patients had HPV 16/18 DNA compared with 27[percent] of noncancer control subjects, which had undergone thoracic surgery for lung diseases other than \*cancer\*. Also the odds ratio ([similar]10-fold) of HPV16/18 infection of nonsmoking female lung \*cancer\* patients was much higher compared with nonsmoking male lung \*cancer\* patients (odds ratio of [similar]2). Additionally, HPV 16/18 DNA was uniformly located in lung \*tumor\* cells, but not in the adjacent noninvolved lung. These results strongly suggest that HPV infection with virus subtypes known to be oncogenic for cervical \*cancer\* is associated with lung \*cancer\* development of nonsmoking Taiwanese female lung \*cancer\* patients. Because oncogenic HPV subtypes encode E6 and E7 viral oncoproteins, which inactivate p53 and Rb protein, respectively, HPV infection provides several key mutations at...

...inactivation of key TSG proteins (166). Although SV40 is definitely involved in the pathogenesis of mesotheliomas, it does not appear to be involved in lung \*cancer\* pathogenesis.

Jaagsiekte sheep retrovirus (JSRV) can induce rapid, multifocal lung \*cancer\* in sheep, but JSRV is a simple retrovirus having no known oncogenes so the mechanism of oncogenesis is still unknown. Recently, HYAL2, a glycosylphosphatidylinositol...

...JSRV (167). Of great interest is the fact that the HYAL2 gene resides in the 600-kb 3p21.3 TSG homozygous deletion region (55). Lung \*cancer\* induced by JSRV closely resembles human bronchiolo-alveolar carcinoma. Further studies are necessary to investigate the relationship of JSRV oncogenesis to human bronchiolo-alveolar carcinoma.

#### SECOND PRIMARY LUNG CANCERS

The risk of developing a second lung \*cancer\* in patients who survived resection of NSCLC is approximately 1-2[percent] per patient per year (168). The average risk of developing a second lung \*cancer\* in patients who survived SCLC is approximately 6[percent] per patient per year (168). Because of the high risk of developing a second lung \*cancer\*, these patients need to be followed carefully for many years. This increased risk probably represents a persistent field defect in the respiratory epithelium of patients cured of one lung \*cancer\*. This defect probably involves the multiple somatically acquired genetic changes detected in respiratory epithelium described previously that predispose these individuals to lung \*cancer\* development. In a related scenario, molecular changes including p53 and KRAS mutations and analysis of LOH and microsatellite alterations at nine chromosomal regions were investigated...although future research is necessary to address the possible contribution of these alterations to the pathogenesis of second primary lung cancers.

#### PROGNOSTIC MARKERS IN LUNG \*CANCER\*

A recent study (170) investigated a panel of nine molecular markers

including p53, Bcl-2, ErbB-2 (HER-2/neu), KI-67, RB, EGFR, factor...  
 ...RB, CD-44, and factor VIII were of prognostic significance. Sabel et al. (171) reported a negative impact of CD40 expression on survival of lung \*cancer\* patients. Cyclin E is a G1 cyclin and one of the key regulators of the G1-S transition. The expression of cyclin E was investigated by immunohistochemistry in a large series of NSCLCs (172). High-cylin E expression was found more frequently in \*tumors\* from smokers than from nonsmokers, in squamous cell carcinomas than in nonsquamous carcinomas, and in later-stage (pT2-4) \*tumors\* than in early-stage (pT1) \*tumors\*. Additionally, patients whose \*tumors\* showed high-level cyclin E expression survived a significantly shorter time than patients with \*tumors\* having low-level expression. However, other CDK2-associated cyclins, including cyclin E2, cyclin A1, and cyclin A2, do not have a prognostic role in NSCLC (173).

#### CONCLUSIONS

The understanding of lung \*cancer\* pathogenesis has grown rapidly over the recent years, but our knowledge will grow even more in the next decade with the information from the Human...

...Project. The use of techniques such as microarrays for testing expression of nearly all human genes and their isoforms at the same time in lung \*cancer\*, or other genome-wide strategies involving proteionomics, will provide large amounts of information that need to be translated into clinical practice and integrated into our understanding of lung \*cancer\* pathogenesis. The main goals for future studies should focus on how this information can be used in terms of risk assessment, prevention, early detection of lung \*cancer\*, and development of new therapeutic targets. New \*treatment\* strategies including drugs that block oncogene functions such as tyrosine kinase inhibitors, gene therapy, monoclonal \*antibodies\* against growth factors and receptors, angiogenesis inhibitors, vaccines, apoptosis modulators, demethylating agents, and new drugs targeted at abnormal pathways are being developed and introduced into clinical trials. These approaches should help to decrease the number of lung \*cancer\* deaths through early detection and \*treatment\* and increase the cure and prolong the survival of patients with lung \*cancer\*.

#### Added material

Sabine Zochbauer-Muller<sup>1</sup>, Adi F. Gazdar<sup>1,2</sup>, and John D. Minna<sup>1,3,4</sup>  
<sup>1</sup> Hamon Center for Therapeutic Oncology Research, Departments of 2...

...UTSouthwestern.edu; John.Minna@UTSouthwestern.edu

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TABLE 1 Major molecular abnormalities in the pathogenesis of lung \*cancer\*

#### FOOTNOTE

a Frequent allele loss at chromosomal sites 1p13, 1p36, 3p14-cen, 3p21.3-22, 3p25-26, 4p15.1-15.3, 4q25-26, 4q33-34...

...8	ND	
GSTP1	7-9	ND
BRCA1	4	ND

p73	0	ND
hMLH1	0	ND
p15	0	ND

#### FOOTNOTES

a Most SCLC data are from \*tumor\* cell lines because of the clinical difficulty in getting pretreatment \*tumor\* samples for study. ND, not done; NSCLC, non-small cell lung \*cancer\*; SCLC, small cell lung \*cancer\*; APC, adenomatous polyposis coli; CDH13, H-cadherin; RARb, retinoic acid receptor b-2; FHIT, fragile histidine triad; TIMP-3, tissue inhibitor of metalloproteinase-3; p16, p16INK4a; MGMT, O6-methylguanine-DNA methyltransferase; DAPK, death-associated protein kinase; ECAD, E-cadherin; GSTP1, glutathione-S-transferase P1; p14, p14ARF; p15, p15INK4b. Data \*extracted\* from references 56-58, 63, 74, 105-107, 120, 122-126.

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7/3,K/9 (Item 1 from file: 135)

DIALOG(R)File 135:NewsRx Weekly Reports

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**Patent issued covering novel CpG oligonucleotides**

Biotech Week, October 2, 2002, p.52

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TEXT: Hybridon, Inc., (HYBN.OB) announced the issuance of U.S. Patent No. 6,426,334 claiming a novel class of CpG oligonucleotides for the \*treatment\* of \*cancer\*.

"The issuance of this patent makes Hybridon a leader in creating second-generation CpG Immunomodulatory Oligonucleotides (IMO)," said James B. Wyngaarden, MD, Hybridon's chairman...

The patent, entitled "Oligonucleotide Mediated Specific \*Cytokine\* Induction and Reduction of \*Tumor\* Growth in a Mammal," covers a method for using \*CpG\* oligonucleotides containing four contiguous guanosines for reducing \*tumor\* growth in mammals. These oligonucleotides induce various \*cytokines\*, including interleukin-12 and interferons. The inventors of the patent are Sudhir Agrawal, D.Phil., Hybridon's president and chief scientific officer, and Qiuyan Zhao...

...compounds that mimic bacterial DNA that activate the human immune system to fight diseases. Independent reports have shown that CpG oligonucleotides are useful in the \*treatment\* of \*cancer\*, infectious diseases, and asthma/allergies, either alone or in combination with antigens, \*antibodies\*, or conventional therapies.

This article was prepared by Biotech Week editors from staff and other

reports.

7/3,K/10 (Item 1 from file: 144)  
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16689323 PASCAL No.: 04-0341947  
**Hypomethylation of DNA and the insulin-like growth factor-II gene in dichloroacetic and trichloroacetic acid-promoted mouse liver \*tumors\***  
LIANHUI TAO; YINGZHE LI; KRAMER Paula M; WEI WANG; PEREIRA Michael A  
Department of Pathology, Medical College of Ohio, 3055 Arlington Avenue,  
Toledo, OH 43614-5806, United States  
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**Hypomethylation of DNA and the insulin-like growth factor-II gene in dichloroacetic and trichloroacetic acid-promoted mouse liver \*tumors\***  
Dichloroacetic acid (DCA) and trichloroacetic acid (TCA) are mouse liver carcinogens. DNA hypomethylation is a common molecular event in \*cancer\* that is induced by DCA and TCA. Hypomethylation of DNA and the insulin-like growth factor-II (IGF-II) gene was determined in DCA- and TCA-promoted liver \*tumors\*. Mouse liver \*tumors\* were initiated by N-methyl-N-nitrosourea and promoted by either DCA or TCA. By dot-blot analysis using an \*antibody\* for 5-methylcytosine, the DNA in DCA- and TCA-promoted \*tumors\* was demonstrated to be hypomethylated. The methylation status of 28 \*CpG\* sites in the differentially methylated region-2 (DMR-2) of mouse IGF-II gene was determined. In liver, 79.3  $\pm$  1.7% of the sites were methylated, while in DCA- and TCA-\*treated\* mice, only 46.4  $\pm$  2.1% and 58.0  $\pm$  1.7% of them were methylated and 8.7  $\pm$  2.6% and 10.7  $\pm$  7.4% were methylated in \*tumors\*. The decreased methylation found in liver from mice exposed to DCA or TCA occurred only in the upstream region of DMR-2, while in \*tumors\* it occurred throughout the probed region. mRNA expression of the IGF-II gene was increased in DCA- and TCA-promoted liver \*tumors\* but not in non-involved liver from DCA- and TCA-exposed mice. The results support the hypothesis that DNA hypomethylation is involved in the mechanism for the \*tumorigenicity\* of DCA and TCA.

English Descriptors: Methylation; DNA; Insulin like growth factor; Gene; Genetics; Animal; Mouse; Liver; \*Tumor\*; \*Cytokine\*; Messenger RNA

French Descriptors: Methylation; DNA; Facteur croissance IGF; Gene; Genetique; Animal; Souris; Foie; Tumeur; \*Cytokine\*; RNA messenger

Spanish Descriptors: Metilacion; DNA; Factor crecimiento IGF; Gen; Genetica; Animal; Raton; Hgado; \*Tumor\*; Citoquina; RNA mensajero

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**Rational Design of Therapeutic Vaccines for CEA+ \*Tumors\***  
PRINCIPAL INVESTIGATOR: CHATTERJEE, MALAYA B



ADDRESS: MALAYA.CHATTERJEE@UC.EDU UNIVERSITY OF CINCINNATI P O BOX 670508  
CINCINNATI, OH 45267

PERFORMING ORG.: UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

DATES: 2009/30/03 TO 2008/31/08 FY : 2004

**Rational Design of Therapeutic Vaccines for CEA+ \*Tumors\***

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

SUMMARY: DESCRIPTION (provided by applicant): Extensive preclinical studies, as well as results obtained from clinical trials, suggest that vaccination with an anti-idiotypic (Id) \*antibody\* (3H1) that mimics an epitope of human carcinoembryonic antigen (CEA) has the potential to augment survival benefits. Anti-Id 3H1 breaks immune tolerance to CEA and induces anti-CEA \*antibody\* as well as CD4+T helper (Th1) responses in colorectal \*cancer\* patients and also in mice transgenic for CEA. This anti-Id approach in its current form, although promising, will need improvements to realize its full potential. Suitable murine \*tumor\* models will be used to explore strategies that will significantly improve the therapeutic impact of this vaccine. The proposal is based on the hypothesis that...

... T-help, in the host, will provide critical help for priming and activation of CEA-specific CTL, the major effector cells (CD8+ T cells) for \*tumor\* destruction. We hypothesize that the combination of CD4+ with CD8+ T cell epitopes will further augment the anti-\*tumor\* immune responses. The specific aims of this proposal are: 1) to determine whether vaccination with 3H1, which will generate anti-CEA Ab and T-help, in combination with mRNA derived from CEA, using dendritic cells (DC) as APC, will induce CTL and engender therapeutic immunity in an established \*tumor\* model in C57BL/6 mice (H2kb), double transgenic for human CEA and HLA-A2; 2) to explore whether a combination of 3H1 with HLA-A2 restricted known agonist CTL epitopes of CEA, using DC as APC, will work better in the above \*tumor\* model; 3) to test whether the idio-peptides, (LCD-2 and CEA-B) derived from the structure of 3H1 and CEA based on the amino...

... the agonist CTL peptides of CEA. The criteria for selection of the optimal regimen for vaccination will be based on the ability to invoke anti-\*tumor\* activities in vitro and in vivo. We will measure the \*antibody\* titer, in vitro CTL activity, intra-cellular \*cytokine\* levels and in vivo \*tumor\* regression. In Aim 4, we will further explore methods to boost \*tumor\*-specific CD4+ as well as CD8+ T cell responses in vivo by coadministration of agents such as IL-2, IL-12, \*CpG\* ODN or anti-CTLA4 \*antibody\*. We will test for any possible autoimmune responses in CEA-expressing normal organs of mice by histopathological analysis (Aim 5). Promising strategies indicated by these...

... in Aim 6 in the murine Apc knock-out transgenic mice expressing CEA and HLA-A2, which arguably, are the best murine model for colon \*cancer\*, as it closely resembles the human disease. The results obtained from these studies will help design improved therapeutic vaccines for the \*treatment\* of CEA+ \*tumors\* and can be incorporated readily into our ongoing clinical programs.

DESCRIPTORS: laboratory mouse; immune tolerance /unresponsiveness; anti-idiotypic \*antibody\*; carcinoembryonic antigen; neoplasm /\*cancer\* immunotherapy; colon neoplasm; nonhuman therapy evaluation; neoplasm / \*cancer\* vaccine; vaccine development

DIALOG(R) File 266:FEDRIP

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IDENTIFYING NO.: 5R01CA083856-04 AGENCY CODE: CRISP

**NOVEL STRATEGIES FOR THE IMMUNOTHERAPY OF COLON \*CANCER\***

PRINCIPAL INVESTIGATOR: REISFELD, RALPH A

ADDRESS: reisfeld@scripps.edu DEPARTMENT OF IMMUNOLOGY ROOM 218 IMM-13 LA JOLLA, CA 92037

PERFORMING ORG.: SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

DATES: 2005/08/00 TO 2004/30/05 FY : 2003

**NOVEL STRATEGIES FOR THE IMMUNOTHERAPY OF COLON \*CANCER\***

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

...SUMMARY: human CEA-based DNA vaccines for the effective immunotherapy of colon carcinoma. The investigators will test the hypothesis that peripheral T cell tolerance to these \*tumor\* self-antigens can be overcome by DNA vaccines boosted by effective adjuvants designed to generate cytolytic T lymphocyte (CTLs) specific for CEA epitopes expressed as...

... either transgenic for CEA or double transgenic for CEA and HLA-A2.1Kb. Their aim is to use such models for optimization of vaccine by \*antibody\*-  
\*cytokine\* fusion proteins and to investigate basic concepts such as mechanisms of T cell co-stimulation, generation of \*tumor\*-specific CTLs and T memory cells and establish principles for adoptive immunotherapy. The specific aims designed to achieve these objectives are: 1) construction of optimal...

... a string of beads or direct targeting of single CEA or repeat epitopes to the endoplasmic reticulum; 3) achievement of optimal adjuvanticity using either unmethylated \*CpG\* dinucleotide motifs or CD40 Ligand/Trimer co-expression; and 4) determination whether \*antibody\*-IL2 fusion proteins can effectively boost DNA vaccines to achieve optimal, long-lived \*tumor\*-protective immunity, as well as eradicate established metastases, and identification of immunological mechanisms involved in generating \*tumor\*-specific CTLs and T memory cells. The achievement of this proposal's objectives should lead to the design of effective DNA vaccines based on rational immunological principles that may ultimately lead to the improved \*treatment\* of colon \*cancer\*.

DESCRIPTORS: laboratory mouse; genetically modified animal; Listeria; Salmonella typhimurium; cytotoxic T lymphocyte; passive immunization; antigen presentation; carcinoembryonal antigen; disease /disorder model; neoplasm /\*cancer\* immunotherapy; neoplasm /\*cancer\* immunology; colon neoplasm; ubiquitin; chimeric protein; nonhuman therapy evaluation; neoplasm /\*cancer\* vaccine; proteasome; vaccine development; vector vaccine

7/3,K/13 (Item 1 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0364877 DBR Accession No.: 2005-10581 PATENT

**Modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection by providing a host cell with a thioaptamer that modifies the activity of a DNA-binding protein involved in an immune response - involving vector-mediated gene transfer and expression in host cell for therapy**

AUTHOR: GORENSTEIN D G; LUXON B A; HERZOG N; ARONSON J F; BEASLEY D;

BARRET A; SHOPE R E; YANG X B  
PATENT ASSIGNEE: UNIV TEXAS SYSTEM 2005  
PATENT NUMBER: WO 200518537 PATENT DATE: 20050303 WPI ACCESSION NO.:  
2005-196216 (200520)  
PRIORITY APPLIC. NO.: US 472888 APPLIC. DATE: 20030523  
NATIONAL APPLIC. NO.: WO 2004US16246 APPLIC. DATE: 20040520  
LANGUAGE: English

**Modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection by providing a host cell with a thioaptamer that modifies the activity of a DNA-binding protein involved in an...**

...ABSTRACT: a transcription factor involved in T cell activation where at least a portion of at least one nucleotide is thiophosphate-modified; (6) a method of \*treating\* a hemorrhagic viral infection; (7) a method of \*treating\* a neuropathologic viral infection; and (8) a method for enhancing vaccine efficacy. BIOTECHNOLOGY - Preferred Method: Modifying an immune response comprises providing a host cell with...

...cell immune response. The modification of the immune response is a shift in a Th1 to Th2 ratio. The immune response is to bacteria, fungus, \*cancer\*, self-antigen, heterologous antigen, retrovirus, hemorrhagic virus or neuropathologic virus. The immune response is in vivo. The thioaptamer modifies \*antibody\* production or cytotoxic T cell activation. Modifying an immune response comprises administering to a host a composition comprising an antigen and one or more partially...

... protein. The composition further comprises IL-1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12 or 13, Type I Interferon, Type II Interferon, \*tumor\* necrosis factor alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), lymphotoxin migration inhibition factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte-macrophage CSF...

... immunity activator. The helper T cell response is in vivo. The helper T cell response comprises a T helper 1-type or 2-type response. \*Treating\* a hemorrhagic viral infection comprises identifying a patient suspected of being infected with a hemorrhagic virus and providing the patient with a therapeutic amount of...

... Ebola virus, Marburg virus, yellow fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus, Rift Valley fever virus or Congo-Crimean hemorrhagic fever virus. \*Treating\* a neuropathologic viral infection comprises identifying a patient suspected of being infected with a neuropathologic virus and providing the patient with a therapeutic amount of...

... DNA binding protein and an antigen. The method further comprises a carrier molecule, comprising liposomes, microcapsules and/or microspheres. The immune response is to a \*cancer\*, allergic rhinitis, eczema, urticaria, anaphylaxis, transplant rejection, systemic lupus erythematosus, rheumatoid arthritis, seronegative spondyloarthritides, Sjogren's syndrome, systemic sclerosis, polymyositis, dermatomyositis, Type I Diabetes Mellitus, Acquired Immune Deficiency Syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, polyendocrine autoimmune disease, hepatitis, sclerosing cholangitis, primary biliary cirrhosis, pernicious anemia, celiac disease, \*antibody\*-mediated nephritis, glomerulonephritis, Wegener's granulomatosis, microscopic polyarteritis, polyarteritis nodosa, pemphigus, dermatitis herpetiformis, psoriasis, vitiligo, multiple sclerosis, encephalomyelitis, Guillain-Barre syndrome, Myasthenia

Gravis, Lambert-Eaton...

... of the thioaptamer is thio-modified. The vaccine comprises one or more pharmaceutically acceptable salts. The antigen comprises a virus, a bacterium, a fungus, a \*cancer\*, a self-antigen, a heterologous antigen, a retrovirus, a hemorrhagic virus or a neuropathologic virus. The antigen comprises a West Nile Virus. The vaccine is...

... or dissolved form. The antigen comprises a live-attenuated or heat-inactivated antigen. The antigen comprises a pathogen-associated molecular pattern antigen, which is a \*CpG\* molecule or polysaccharide. The thioaptamer comprises a concatenated aptamer comprising one or more concatenated thioaptamers. The protein that the thioaptamer binds specifically with comprises a...

... receptor 2 or 4. **ACTIVITY** - Virucide. No biological data given. **MECHANISM OF ACTION** - Vaccine. **USE** - The method is useful in modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection (claimed). **ADMINISTRATION** - The composition is administered via oral or parenteral route (claimed). No dosage given. (72 pages)

**DESCRIPTORS:** recombinant interferon, \*tumor\* necrosis factor, granulocyte-macrophage colony stimulating factor, vascular endothelial cell growth factor prep., isol., vector-mediated gene transfer, expression in host cell, aptamer, appl., hemorrhagic disorder, neuropathologic virus infection therapy, recombinant vaccine prep. virucide antitumor immunostimulant protein lymphokine \*cytokine\* leukocyte (24, 16)

7/3,K/14 (Item 2 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0360920 DBR Accession No.: 2005-06624 PATENT

**Detecting/detecting and distinguishing between or among prostate cell proliferative disorders or their stages in a subject, useful for \*treating\* prostate \*cancer\*, by determining gene expression level of e.g. supervillin (SVIL) - involving vector-mediated gene transfer and expression in host cell for gene therapy**

**AUTHOR:** VANAJA D K; YOUNG C Y F

**PATENT ASSIGNEE:** MAYO FOUND MEDICAL EDUCATION and RES 2005

**PATENT NUMBER:** WO 200507830 **PATENT DATE:** 20050127 **WPI ACCESSION NO.:**

2005-102097 -(200511)

**PRIORITY APPLIC. NO.:** US 487553 **APPLIC. DATE:** 20030714

**NATIONAL APPLIC. NO.:** WO 2004US22850 **APPLIC. DATE:** 20040714

**LANGUAGE:** English

**Detecting/detecting and distinguishing between or among prostate cell proliferative disorders or their stages in a subject, useful for \*treating\* prostate \*cancer\*, by determining gene expression level of e.g. supervillin (SVIL) - involving vector-mediated gene transfer and expression in host cell for gene therapy**

...**ABSTRACT:** among prostate cell proliferative disorders or their stages is, at least in part, afforded. **INDEPENDENT CLAIMS** are also included for the following: (1) an isolated \*treated\* nucleic acid derived from SEQ ID NOS: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treatment\* is to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of

- hybridization; (2) a nucleic acid, comprising at least 16 contiguous nucleotides of a \*treated\* genomic DNA sequence derived from a sequence selected from SEQ ID NOS: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treatment\* is to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine...
- ... hybridize under high stringency to them. The polypeptide is detected by at least one method selected from immunoassay, Enzyme-Linked Immunosorbent Assay immunoassay, radioimmunoassay, and \*antibody\*. The expression is determined by detecting the presence or absence of \*CpG\* methylation within the gene or sequence, where hypermethylation indicates the presence of, or stage of the prostate cell proliferative disorder. Expression is of at least...
  - ... DNA; and contacting genomic DNA obtained from the subject with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated \*CpG\* dinucleotides within at least one target region of the genomic DNA, where the target region comprises, or hybridizes under stringent conditions to at least 16...
  - ... 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the contiguous nucleotides comprise at least one \*CpG\* dinucleotide sequence, and where detecting, or detecting and distinguishing between or among colon cell proliferative disorders or stages is, at least in part, afforded. Normal...
  - ... intermediate, T2, Gleason score 6 lymph node positive and negative; high grade, T3, Gleason score 9 lymph node positive and negative; prostatic adenocarcinoma; and metastatic \*tumors\*. Adjacent benign tissue is distinguished from at least one condition selected from intermediate, T2, Gleason score 6 lymph node positive and negative; high grade, T3, Gleason score 9 lymph node positive and negative; prostatic adenocarcinoma; and metastatic \*tumors\*, and where the target region comprises, or hybridizes under stringent conditions to at least 16 contiguous nucleotides of a sequence selected from ZNF185 (SEQ ID...
  - ... subject, a biological sample having genomic DNA; contacting the genomic DNA, or its fragment, with one reagent(s) that distinguishes between methylated and non methylated \*CpG\* dinucleotide sequences within at least one target sequence of the genomic DNA, or its fragment, where the target sequence comprises, or hybridizes under stringent conditions ...
  - ... 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, the contiguous nucleotides comprising at least one \*CpG\* dinucleotide sequence; and determining, based at least in part on the distinguishing, the methylation state of at least one target \*CpG\* dinucleotide sequence, or an average, or a value reflecting an average methylation state of target \*CpG\* dinucleotide sequences, where detecting, or detecting and distinguishing between or among prostate cell proliferative disorders or stages thereof is, at least in part, afforded. Detecting...
  - ... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. Distinguishing between methylated and non methylated \*CpG\* dinucleotide sequences within the target sequence comprises converting unmethylated cytosine bases within

the target sequence to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties. Distinguishing between methylated and non-methylated \*CpG\* dinucleotide sequences within the target sequence(s) comprises methylation state-dependent conversion or non-conversion of at least one \*CpG\* dinucleotide sequence to the corresponding converted or non-converted dinucleotide sequence. The biological sample is selected from cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, ejaculate, urine, blood, and their combinations. Distinguishing between methylated and non methylated \*CpG\* dinucleotide sequences within the target sequence comprises use of at least one nucleic acid molecule or peptide nucleic acid (PNA) molecule comprising, in each case...

... 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements. The contiguous sequence comprises at least one \*CpG\*, TpG or CpA dinucleotide sequence. The method comprises use of at least two such nucleic acid molecules, or PNA molecules. The method comprises use of...

... use of at least four such nucleic acid molecules, PNA molecules. The method may comprise obtaining, from a subject, a biological sample having genomic DNA; \*extracting\* or otherwise isolating the genomic DNA; \*treating\* the genomic DNA, or its fragment, with one or more reagents to convert cytosine bases that are unmethylated in the 5-position thereof to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties; contacting the \*treated\* genomic DNA, or the \*treated\* fragment, with an amplification enzyme and at least two primers comprising, in each case a contiguous sequence of at least 9 nucleotides that is complementary ...

...selected from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treated\* genomic DNA or its fragment is either amplified to produce at least one amplificate, or is not amplified; and determining, based on a presence or absence of, or on a property of the amplificate, the methylation state of at least one \*CpG\* dinucleotide of a sequence selected from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, or an average, or a value reflecting an average methylation state of the \*CpG\* dinucleotides, where at least one of detecting, and detecting and distinguishing between prostate cell proliferative disorders or stages is, at least in part, afforded. \*Treating\* the genomic DNA, or its fragment comprises use of a reagent selected from bisulfite, hydrogen sulfite, disulfite, and their combinations. Contacting or amplifying comprises use...

... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. The method further comprises for the step of contacting the \*treated\* genomic DNA, the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least...

... the amplificate. Contacting or amplifying comprises use of methylation-specific primers. The method comprises, for the contacting step, using primer oligonucleotides comprising one or more \*CpG\*; TpG or CpA dinucleotides; and further comprising, for the determining step, the use of at least one method selected from hybridizing in at least one...

- ... base; and sequencing, in the determining step, of the amplificate. The method comprises, in the contacting step, amplification by primer oligonucleotides comprising one or more \*CpG\*; TpG or CpA dinucleotides and further comprising, in the determining step, hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at...
- ... or hybridizes under stringent conditions to a bisulfite-converted sequence derived. The method may comprise obtaining, from a subject, a biological sample having genomic DNA; \*extracting\* , or otherwise isolating the genomic DNA; contacting the genomic DNA, or its fragment, comprising at least 16 contiguous nucleotides of a sequence selected from SEQ...
- ... determining, based on a presence or absence of, or on property of at least one such cleavage fragment, the methylation state of at least one \*CpG\* dinucleotide of a sequence selected from SEQ ID NOs:1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49,51; and their complements, or an average, or a value reflecting an average methylation state of \*CpG\* dinucleotides, where at least one of detecting, or of detecting and differentiating between or among prostate cell proliferative disorders or stages is, at least in...
- ... from cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, ejaculate, urine, blood, and their combinations. The contiguous base sequence comprises at least one \*CpG\*, TpG or CpA dinucleotide sequence. The \*treatment\* comprises use of a reagent selected from bisulfite, hydrogen sulfite, disulfite, and their combinations. The method comprises use of the kit above. Preferred Oligomer: The oligomer comprises at least one \*CpG\*, CpA or TpG dinucleotide sequence. Preferred Array: The oligomers are bound to a planar solid phase in the form of a lattice selected from linear...
- ... of oligonucleotides is useful for at least one of detection of; detection and differentiation between or among subclasses or stages of; diagnosis of; prognosis of; \*treatment\* of; monitoring of; and \*treatment\* and monitoring of prostate cell proliferative disorders. The nucleic acid, an oligonucleotide or a set of oligonucleotides is useful for detecting, or detecting and distinguishing...
- ... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. The set of oligomers is useful as probes for determining at least one of a cytosine methylation state, and a single nucleotide polymorphism (SNP) of...
- ... oligonucleotides, method of manufacturing, array and kit is useful for detecting, detecting and differentiating between or among subclasses or stages of, diagnosis of, prognosis of, \*treatment\* of, monitoring of, or \*treatment\* and monitoring of prostate cell proliferative disorders (all claimed). The method is useful for improved diagnosis, \*treatment\* and monitoring of prostate cell proliferative disorders, more specifically by enabling the improved identification of and differentiation between subclasses of the disorder or stages of prostate \*tumors\*. ADMINISTRATION - Dosage is 0.01-50 mg/kg body weight via parenteral injection e.g., subcutaneously, intraperitoneally, intravenously or intramuscularly, myocardial, intratumoral, peritumoral, or to the interstitial space of a tissue. EXAMPLE - Total RNA was \*extracted\* from 30 frozen prostate tissue section with Trizol (RTM) reagent. DNA was removed, RNA quality was monitored by agarose

gel electrophoresis and quantitative real-time...

... Erg-2 and RhoGDI-beta were selected for validation. Genomic DNA was obtained from metastatic, primary, matched benign prostatic tissues and modified by sodium bisulfite \*treatment\* by converting unmethylated but not methylated cytosines to uracil. Results showed that a significant decrease in the expression of ZNF185, BPAG1 and PSP94 mRNA levels was observed in metastatic versus organ confined and localized \*tumors\* compared to benign tissues. (178 pages)

DESCRIPTORS: recombinant MARCKS-like protein prep., isol., vector-mediated gene transfer, expression in host cell, DNA array, polymerase chain reaction, appl., prostate \*cancer\* diagnosis, prognosis, therapy, gene therapy microarray DNA amplification \*tumor\* cytostatic DNA sequence protein sequence (24, 10)

...SECTION: DISEASE-\*Cancer\*; DIAGNOSTICS-Molecular Diagnostics...

7/3,K/15 (Item 3 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0359246 DBR Accession No.: 2005-04950 PATENT

**Promoting antigen presentation comprises targeting antigen to dendritic cells using an anti-DEC-205 \*antibody\* - antigen presentation promotion using recombinant \*antibody\* for use in disease therapy and gene therapy**

AUTHOR: HAWIGER D; NUSSENZWEIG M; STEINMAN R M; BONIFAZ L

PATENT ASSIGNEE: HAWIGER D; NUSSENZWEIG M; STEINMAN R M; BONIFAZ L 2004

PATENT NUMBER: US 20040258688 PATENT DATE: 20041223 WPI ACCESSION NO.:

2005-078933 (200509)

PRIORITY APPLIC. NO.: US 800023 APPLIC. DATE: 20040312

NATIONAL APPLIC. NO.: US 800023 APPLIC. DATE: 20040312

LANGUAGE: English

**Promoting antigen presentation comprises targeting antigen to dendritic cells using an anti-DEC-205 \*antibody\* - antigen presentation promotion using recombinant \*antibody\* for use in disease therapy and gene therapy**

...ABSTRACT: a) exposing ex vivo or in vivo dendritic cells from the mammal to either: (i) a conjugate comprising a preselected antigen covalently bound to an \*antibody\* to DEC-205; or (ii) a recombinant anti-DEC-205 \*antibody\* genetically engineered to contain at least one preselected antigen on at least one preselected site on the \*antibody\* molecule; and (b) promoting maturation of the dendritic cells ex vivo or in vivo by combining the antigen/anti-DEC-205 complex of (i) or (ii) of step (a) with a dendritic cell maturation factor. The method may also comprise (M1b) administering a recombinant anti-DEC-205 \*antibody\* and at least one dendritic cell maturation factor to a mammal, where the \*antibody\* has been genetically engineered to contain at least one preselected antigen and at least one dendritic cell maturation factor, each on at least one preselected site on the \*antibody\* molecule. INDEPENDENT CLAIMS are also included for: (1) increasing (M2) the persistence of MHC class I:antigen complexes in a mammal, by performing the steps...

... composition (C1) for inducing long term cellular or humoral immunity in a mammal, comprising: (a) an antigen, prepared by conjugation with an anti-DEC-205 \*antibody\*, or forming part of an engineered anti-DEC-205 \*antibody\*; (b) a dendritic cell maturation factor; and (c) an



adjuvant, where C1 is effective when administered at levels of 10-1000 fold lower than the effective dose of a vaccine which is not conjugated to an anti-DEC-205 \*antibody\* or its fragments, and which is not administered with a dendritic cell maturation factor, but for which an adjuvant is required; (3) an immunogenic composition...

... but further comprising a delivery means; (4) a DNA vaccine composition (C3); (5) protection (M3) of a mammal from infection with a pathogen or a \*tumor\* cell; (6) long term protection (M3) of a mammal from infection with a pathogen or a \*tumor\* cell; (7) a virus-like particle (VLP) comprising at least one immunogenic polypeptide from a virus against which immunity is desired; (8) immunizing (M5) a...

... composition (C4) and (10) a recombinant anti-DEC-205 molecule (II) BIOTECHNOLOGY - Preferred Method: In (a) or (b) of M1, the preselected site on the \*antibody\* is on the heavy or light chain of the \*antibody\*, or on their fragments. M1 results in induction of a long term cellular and/or humoral immune response in the mammal. M1 results in the...

... response and in expanding antigen-specific CD4+ and CD8+ T cells in the mammal, as compared to an antigen administered without an anti-DEC-205 \*antibody\* and without a dendritic cell maturation factor. M1 increases the efficiency with which the antigen initiates CD4+ and CD8+ immunity from the polyclonal naive T cell repertoire in vivo. The anti-DEC-205 \*antibody\* is polyclonal or monoclonal \*antibody\*. The \*antibody\* is chosen from a human \*antibody\*, a murine \*antibody\* that reacts with human DEC-205 protein, a humanized \*antibody\* and a human-chimerized \*antibody\*. The \*antibody\* is a monovalent or single chain \*antibody\*. The T cell response is chosen from cytolytic T cell response, helper T cell response and memory T cell response. M1 results in priming of CD8+ T cells specific for the preselected antigen, which is a non-replicating and/or subunit vaccine. The vaccine is composed of antigens chosen from \*tumor\* vaccine, viral vaccine, bacterial vaccine and vaccines for other pathogenic organisms for which a long lasting immune response is necessary to provide long term protection from infection or disease. The viral vaccine is chosen from a DNA viral vaccine, an RNA viral vaccine or retroviral vaccine formed with the \*antibody\* combining function of the anti-DEC-205 \*antibody\*. The vaccine is administered as a single dose, which is preferably sufficient to elicit a long-lasting immune response. The vaccine is effective when administered...

... single dose of vaccine, when administered at levels of 10-1000 fold lower than the level of a vaccine administered without an anti-DEC-205 \*antibody\* and without a dendritic cell maturation factor but with an adjuvant, results in highly efficient antigen presentation and induction of long lasting immune responses. The...

... T cell response, helper T cell response and memory T cell response. M1 results in induction of mucosal immunity specific for the predetermined antigen. The \*treatment\* of a mammal with the \*tumor\* vaccine results in \*tumor\* regression in vivo, where the \*tumor\* regression is associated with an increase in a \*tumor\* specific CD8+ cytolytic T cell response. In M2 the MHC class I:antigen complexes persist in vivo in multiple lymphoid sites from 15-30 days. In any one of M1-M4, the dendritic cell maturation factor is chosen from an anti-CD40 \*antibody\*, an inflammatory \*cytokine\*, a poly I/C, a single strand RNA, DNA, \*CpG\*, ligation of the interleukin-1 (IL-1), TNF or TOLL-like receptor families, and activation of an intracellular pathway leading to dendritic cell maturation such as TNF receptor-associated factor-6

(TRAF-6) or NF-kappaB. Protection (M3) of a mammal from infection with a pathogen or a \*tumor\* cell, comprises administering a vaccine comprising: (a) a vector (V1) containing a gene encoding a protein or polypeptide from a pathogen or \*tumor\* cell or its immunogenic fragment; (b) a vector (V2) containing a gene encoding the light or heavy chain anti-DEC-205 \*antibody\*; (c) a vector (V3) containing a gene encoding a dendritic cell maturation factor; and (d) an adjuvant. Long term protection (M4) of a mammal from infection with a pathogen or a \*tumor\* cell, comprises administering a vaccine comprising: (a) vector (V1); (b) vector (V2); (c) an adjuvant; and (d) a dendritic cell maturation factor. Preferred Composition: The...

... C3) comprises: (a) an isolated DNA molecule having one or more nucleotide sequence encoding at least one antigenic polypeptide isolated from a virus, bacterium or \*tumor\* cell; (b) an isolated DNA molecule comprising at least one nucleotide sequence encoding an anti-DEC-205 \*antibody\* or its DEC-205 binding fragment, and (c) a carrier. The composition when administered with a dendritic cell maturation factor at levels of 10-1000 fold lower than the effective dose of an antigenic polypeptide which is not conjugated to an anti-DEC-205 \*antibody\* or its fragments, and which is not administered with a dendritic cell maturation factor, but requires an adjuvant, results in efficient, vigorous and long lasting cellular and humoral immunity specific for the virus, bacterium or \*tumor\* cell. The sequence encoding an anti-DEC-205 \*antibody\* (fragment) is preferably selected from SEQ ID NOS 13 (330 bp) and 14 (354 bp). (C4) comprises a nucleic acid molecule comprising: (a) a first nucleotide sequence encoding a chain of \*antibody\* specific for DEC-205; (b) a second nucleotide sequence encoding at least one antigen from a virus, bacterium or \*tumor\* cell against which immunity is desired; (c) a third nucleotide sequence encoding a dendritic cell maturation factor; and (d) a fourth nucleotide sequence comprising a promoter for expression of a fusion protein comprising the anti-DEC-205 \*antibody\*, the antigen and the dendritic cell maturation factor; and (e) a carrier. Preferred Agent: The virus-like particle (I) comprises: (a) at least one immunogenic polypeptide from a virus against which immunity is desired conjugated to monovalent fragments of an anti-DEC-205 \*antibody\*; (b) a dendritic cell maturation factor; and (c) an adjuvant. (I), when administered at an immunogenically effective amount with a dendritic cell maturation factor at...

... 10-1000 fold lower than the effective dose of a virus-like particle where the immunogenic polypeptide is not conjugated to an anti-DEC-205 \*antibody\*, and is not administered with a dendritic cell maturation factor, results in efficient and long lasting cellular and humoral immunity specific for the virus. The...

... the virus-like particle results in long term T cell, B cell or mucosal immunity. Preferred Molecule: The recombinant anti-DEC-205 molecule comprises an \*antibody\* reactive with DEC-205 which has been genetically modified to contain at least one preselected antigen on at least one site on the \*antibody\* molecule, and at least one dendritic cell maturation factor at least one site on the \*antibody\* molecule, where the \*antibody\* molecule, upon administration to a mammal, is capable of delivering the antigen to antigen presenting cells expressing DEC-205, and the delivery results in highly...

... antigen was effective in generating protective immunity, including the mucosal surface. USE - The methods and compositions are useful for immunizing a mammal to prevent or \*treat\* a disease such as a viral, bacterial or other infection or \*cancer\*. The immunization preferably results in induction of long term T cell, B cell or mucosal immunity

(all claimed). Compositions of the invention that lack a...

... 1-10 microgram or 10-100 ng (claimed). ADVANTAGE - The antigen is targeted to antigen presenting cells through the inclusion of the anti-DEC-205 \*antibody\*, making antigen presentation highly efficient. The immunity induced is robust and long lasting, even from a single dose at low concentration. EXAMPLE - No relevant example...

DESCRIPTORS: antigen presentation promotion in mammal, dendrite cell maturation, DEC-205 recombinant monoclonal \*antibody\*, humanized \*antibody\*, chimeric \*antibody\*, single chain \*antibody\*, virus-like particle, expression vector, fusion protein, RNA vaccine, nucleic acid vaccine, appl. virus, bacterium infection, \*cancer\* therapy, antigen tolerance induction, gene therapy animal \*antibody\* \*antibody\* engineering cytostatic virucide \*tumor\* (24, 08)

...SECTION: GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques and Analysis; PHARMACEUTICALS-\*Antibodies\*...

...THERAPEUTICS-Gene Therapy; DISEASE-\*Cancer\*-

7/3,K/16 (Item 4 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0356875 DBR Accession No.: 2005-02579 PATENT

**In vitro diagnosis of \*cancer\*, based on detecting hypomethylation of deoxycytidine in CpG doublets present in specific sequences from the B melanoma antigen locus - method of \*cancer\* diagnosis involving detection of DNA methylation using an \*antibody\***

AUTHOR: DE SARIO A; GRUNAU C

PATENT ASSIGNEE: CNRS CENT NAT RECH SCI 2004

PATENT NUMBER: FR 2854903 PATENT DATE: 20041119 WPI ACCESSION NO.: 2004-824589 (200482)

PRIORITY APPLIC. NO.: FR 20035730 APPLIC. DATE: 20030513

NATIONAL APPLIC. NO.: FR 20035730 APPLIC. DATE: 20030513

LANGUAGE: French

**In vitro diagnosis of \*cancer\*, based on detecting hypomethylation of deoxycytidine in CpG doublets present in specific sequences from the B melanoma antigen locus - method of \*cancer\* diagnosis involving detection of DNA methylation using an \*antibody\***

ABSTRACT: DERWENT ABSTRACT: NOVELTY - In vitro diagnosis of cancers, other than testicular \*tumors\*, in humans and animals by detecting a reduced level of methylation of deoxycytidine in specific sequences from the BAGE (B melanoma antigen) locus. DETAILED DESCRIPTION - In vitro diagnosis of cancers, other than testicular \*tumors\*, in humans and animals comprises: (1) \*extracting\* total DNA from cells of a biological sample; (2) measuring methylation at position 5 of the pyrimidine ring in deoxycytidine (dC) residues in 5'-\*CpG\*-3' doublets in specific sequences (A) from the BAGE locus; (3) comparing the level of methylation with that determined in a similar DNA \*extract\* from non-cancerous tissue; and (4) correlating a lower level of methylation in the test sample with diagnosis of \*cancer\*. (A) is any of: (a) 13 sequences reproduced (of 1273 to 243 nucleotides); (b) fragments of (a) containing at least one \*CpG\*, or (c) derivatives of (a) and (b) with at least 90% homology, containing at least one \*CpG\* and able to hybridize to (a) or (b), particularly in 5 x SSPE buffer at 55 degreesC. INDEPENDENT CLAIMS are also included for: (1) the 13 specified sequences (A) and their fragments containing at least one

\*CpG\* ; (2) primers pairs (14)/(15) and (16)/(17) for amplification of (A) or their fragments; and (3) kit for the new process comprising at least...

... depending on the primer pair used. tttagaggattaggagaagggggagt (14)  
acctaccaattaacattattactaacatta (15) gatgggtgggtgtaatatagatggt (16)  
ccttaaacaatatataaacctataataa (17) BIOTECHNOLOGY - Preferred Process: The degree of methylation is determined by: (a) \*treating\* the \*extracted\* DNA with sodium bisulfite to convert non-methylated dC to deoxyuridine (dU), without altering methylated dC; (b) amplification, especially by PCR, of all sequences (A...

... cloning and sequencing, or by digestion with a restriction enzyme (RE) that either has a recognition site that includes a dC of one or more \*CpG\* or does not cut an amplified sequences that contains dC in doublets. Any fragments formed are separated by electrophoresis and the amount of fragment determined...

... of the electrophoretic band and comparison with a reference curve, established using similar sequences that have been 0-100% methylated using a methylation reagent (especially \*CpG\* methylase M.SssI). Alternatively, determination comprises \*treating\* amplicons with a methylation reagent then quantification of methylated dC using a labeled anti-methylated dC \*antibody\*, and comparison with a standard curve, as above. Preferred RE are MboI, AclI and HphI and the specification lists cutting sites, in (A), for these enzymes. Preferred Materials: In (A), dC residues that are not part of a \*CpG\* doublet are replaced by dU or deoxythymidine, and optionally also at least one (up to all) dC in the doublets is/are replaced similarly. USE - The method is used for diagnosis of cancers, other than testicular \*tumors\*, in humans or animals. ADVANTAGE - The test material (DNA) is very stable; the process is suitable for automation; and hypomethylation of \*CpG\* in the BAGE locus was detected in all \*tumors\* (melanoma; ovarian \*cancer\* and Wilms \*tumor\* ) analyzed. Testicular tissue was the only normal tissue in which hypomethylation was found.(34 pages)

DESCRIPTORS: DNA methylation, detection, DNA primer, polymerase chain reaction, DNA sequencing, electrophoresis, antidody, appl., \*cancer\*, diagnosis DNA amplification \*tumor\* DNA sequence (24, 04)

SECTION: DIAGNOSTICS-\*Antibody\*-Based Diagnostics...

...GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques and Analysis; DISEASE-\*Cancer\*

7/3,K/17 (Item 5 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0352931 DBR Accession No.: 2004-25223 PATENT

**Novel immunogenic fragment of Cripto polypeptide, useful as vaccine for \*treating\* \*cancer\* e.g. colon, lung, colorectal and breast \*cancer\* - recombinant protein production via plasmid expression in host cell for use in disease therapy**

AUTHOR: CABEZON T E V S; GERARD C M G; PALMANTIER R M; VINALS Y D B C  
PATENT ASSIGNEE: CABEZON T E V S; GERARD C M G; PALMANTIER R M; VINALS Y D B C 2004

PATENT NUMBER: US 20040202648 PATENT DATE: 20041014 WPI ACCESSION NO.: 2004-727978 (200471)

PRIORITY APPLIC. NO.: US 816476 APPLIC. DATE: 20040401

**Novel immunogenic fragment of Cripto polypeptide, useful as vaccine for  
\*treating\* \*cancer\* e.g. colon, lung, colorectal and breast \*cancer\* -  
recombinant protein production via plasmid expression in host cell for  
use in disease therapy**

ABSTRACT: DERWENT ABSTRACT: NOVELTY - An immunogenic fragment (I) of a Cripto polypeptide, being immunologically reactive with an \*antibody\* and/or T-cell that reacts with a polypeptide having any one of two fully defined sequences (S1) of 188 amino acids as given in...

... at least 20 contiguous amino acids in length, is new. DETAILED DESCRIPTION - An immunogenic fragment (I) of a Cripto polypeptide, being immunologically reactive with an \*antibody\* and/or T-cell that reacts with a polypeptide having any one of two fully defined sequences (S1) of 188 amino acids as given in...

... comprising (I); (6) an isolated T cell population (VII) comprising T cells prepared by stimulating cells using (I); (7) inhibiting (M1) the development of a \*cancer\* in a patient, involves incubating CD4+ and/or CD8+ T cells isolated from a patient with (S2) and administering to the patient an effective amount of the T cells, and thereby inhibiting the development of a \*cancer\* in the patient; (8) producing (M2) an immunogenic response to Cripto in an animal involves administering a first component comprising a polynucleotide encoding (S2) and...

... protein. Preferred Composition: In (VI), the immunostimulant is a TH-1 inducing adjuvant comprising 3D-MPL, QS21, a mixture of QS21 and cholesterol, and a \*CpG\* oligonucleotide. Preferred Method: (M1) further involves allowing the T cells to proliferate. In (M2), the polynucleotide is recombinant DNA. (M2) further involves admixing the polynucleotide...

... sequence of human Cripto-1. This peptide was coupled to keyhole limpet hemocyanin (KLH) using glutaraldehyde. Two rabbits were each immunized with KLH coupled peptide. \*Antibodies\* were produced in rabbits. Antisera were tested by ELISA against the peptide and the carrier protein. Escherichia coli recombinant protein Cripto-1 (18 Kd) was detected with the sera of rabbits injected with synthetic peptide. Western blots using monoclonal \*antibodies\* to Cripto-1 and rabbit antisera from rabbits injected with the peptide indicated the presence of a single intense polypeptide band at approximately 18 kD in cell \*extract\* as well as cell pellets. In addition, coomassie Blue stained polyacrylamide gel indicated the presence of a polypeptide (approximately 18 kD). No polypeptide having a molecular weight of 18 kD was detected by \*antibodies\*, antisera, or Coomassie Blue stain in the negative control or cellular \*extract\* supernatant. The assessment of immunological recognition of Cripto protein shows that \*antibodies\* recognize the \*tumor\* -associated antigen itself. Finally, an immunostaining study on \*cancer\* tissues using anti-Cripto \*antibodies\* shows Cripto-specific immune response to target cripto naturally expressed in \*cancer\* cells. USE - (VI) is useful for \*treating\* \*cancer\* in a patient, which involves administering (VI) to the patient. (I) is useful for stimulating T cells specific for Cripto, which involves contacting the cells with (I). (M1) is useful for inhibiting the development of a \*cancer\* in a patient. (M3) is useful for inducing an immunoresponse to Cripto in an animal (all claimed). (I) or (VI) is useful for \*treating\* or diagnosing \*cancer\*, preferably

lung, colon, colorectal or breast \*cancer\* . ADMINISTRATION - Administration of (VI) is by parenteral or oral routes at dosages ranging from 25 microg to 5 mg/kg. EXAMPLE - Total RNA was \*extracted\* from snap frozen biopsies or cell lines. Total RNA from normal tissues was also obtained. Poly-A+ mRNA was purified from total RNA after DNase \*treatment\* using oligo-dT magnetic beads. Quantification of the mRNA was performed by spectrofluorimetry. Real-time reactions were assembled according to standard PCR protocols using 2...

... thus suggests the candidate antigen and actin had the same expression level. RT-PCR analysis, using SybrI detection, was performed on a set of colon \*tumor\* and matched normal colon from 6 different patients and 48 normal tissue samples. TaqMan detection was run on a set of colon \*tumor\* and matched normal colon from 6 other patients (reaction were run in triplicates) and 48 normal tissue samples. The results showed that Cripto, while being marginally expressed in normal adult tissues, was highly over-expressed in a majority of colorectal \*tumors\*, with an over-expression rate of more than ten-fold. Cripto was dramatically over-expressed in a lung \*tumor\* cell line (CRL-5815). Cripto \*tumor\* associated antigen was therefore a suitable vaccine candidate to \*treat\* both colorectal and lung \*cancer\* patients. (64 pages)

DESCRIPTORS: human recombinant Cripto protein prep., fusion protein, vector-mediated gene transfer expression in host cell, appl. lung, colon, colorectal, mamma \*cancer\* therapy, diagnosis, immune response induction, recombinant vaccine cytostatic animal mammal \*tumor\* protein sequence DNA sequence (23, 50)

...SECTION: GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques and Analysis; DISEASE-\*Cancer\*-

7/3,K/18 (Item 6 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0348947 DBR Accession No.: 2004-21239 PATENT

**Producing immortalized B memory lymphocytes, useful for \*treating\* \*cancer\* , infectious, inflammatory, autoimmune or allergic diseases, comprises transforming B cells using Epstein Bart Virus in the presence of a polyclonal B cell activator - for use in gene therapy**

AUTHOR: LANZAVECCHIA A

PATENT ASSIGNEE: INST RES IN BIOMEDICINE 2004

PATENT NUMBER: WO 200476677 PATENT DATE: 20040910 WPI ACCESSION NO.:

2004-653426 (200463)

PRIORITY APPLIC. NO.: US 516665 APPLIC. DATE: 20031030

NATIONAL APPLIC. NO.: WO 2004IB1071 APPLIC. DATE: 20040226

LANGUAGE: English

**Producing immortalized B memory lymphocytes, useful for \*treating\* \*cancer\* , infectious, inflammatory, autoimmune or allergic diseases, comprises transforming B cells using Epstein Bart Virus in the presence of a polyclonal B cell activator - for use...**

...ABSTRACT: presence of a polyclonal B cell activator. DETAILED DESCRIPTION - Producing a clone of an immortalized human B memory lymphocyte capable of producing a human monoclonal \*antibody\* with a desired antigen specificity comprises: (a) transforming a population of cells comprising or consisting of human memory B lymphocytes with EBV or using a...

... activator; (b) screening the culture supernatant for antigen

specificity; and (c) isolating an immortalized human B memory lymphocyte clone capable of producing a human monoclonal \*antibody\* having the desired antigen specificity, where the method transforms at least 20% of the human B memory lymphocytes in the population. INDEPENDENT CLAIMS are also included for the following: (1) producing a human monoclonal \*antibody\*; (2) an immortalized B cell clone made by the method described above; (3) a purified neutralizing monoclonal \*antibody\* or \*antibody\* fragment made by the method of (1), where the \*antibody\* recognizes an antigen: (i) from a pathogen, e.g. human immunodeficiency virus, hepatitis A to C virus, herpes simplex virus type 1 or type 2...

... tularensis, Salmonella species, Vibrio cholerae, or toxic Escherichia coli, preferably severe acute respiratory syndrome (SARS) coronavirus; (ii) cocaine, heroin, benzoyllecgonine, or an amphetamine; or (iii) \*tumor\* necrosis factor- $\alpha$  (TNF- $\alpha$ ), beta-amyloid protein, SARS coronavirus spike protein, prion protein PrP, complement C5, CBL, CD147, interleukin (IL)-8, HIV glycoprotein gp120, VLA-4, CD11a, CD18, VEGF, CD40L, an ICAM, a VCAMs, CD80, TPL2, Her2 or an integrin, where the affinity of the interaction between antigen and \*antibody\* is 10<sup>10</sup> M or tighter; (4) a pharmaceutical composition comprising a monoclonal \*antibody\* or \*antibody\* fragment of (3) and a pharmaceutical carrier; (5) a method for \*treating\* a subject; (6) a kit, for diagnosing \*tumor\*, autoimmune or allergic disease based on human monoclonal \*antibodies\* or fragments of (3); (7) a method of preventing transmission of the SARS virus; (8) a method of diagnosing SARS; (9) a method of activating human B memory lymphocytes; (10) a method for preparing a recombinant cell; (11) a method for preparing and obtaining a nucleic acid molecule encoding an \*antibody\* of interest; and (12) a method for preparing an \*antibody\* for pharmaceutical use.

BIOTECHNOLOGY - Preferred Methods: The polyclonal B cell activator is an agonist of a Toll Like Receptor (TLR), which is expressed on memory B cells. The B cell polyclonal Activator is an agonist of TLR-7, TLR-9, or TLR-10. The polyclonal B cell activator is \*CpG\*, R-848 and other imidazoquinoline compounds that stimulate TLRs, CD40L, BAFF, cells that express CD40L or BAFF, or monoclonal \*antibodies\* that mimic the effects of these activators. The polyclonal B cell activator is \*CpG\* oligodeoxynucleotide or \*CpG\* 2006. An additional stimulant of cellular growth and/or differentiation is added during the transformation step. The additional stimulant is a \*cytokine\*, e.g. IL-2 or IL-15. Cloning is carried out using limiting dilution. A subpopulation of human memory B lymphocytes with a specific antigen specificity are selected before the transformation step. The B lymphocyte produces \*antibody\* with antigen specificity that can be selected only by the human immune system. The \*antibody\* is directed against human pathogens or other microbial pathogens and toxins known in the field of microbiology, allergens, \*tumor\* antigens, autoantigens or alloantigens, or chemicals or toxins. The method does not involve cellular fusion of the B memory lymphocytes with other cells. The method transforms at least 50% or at least 80% of the human B memory lymphocytes in the population. Producing a human monoclonal \*antibody\* comprises culturing a clone of all immortalized human B memory lymphocyte produced by the method described above and isolating the human monoclonal \*antibody\*. The method further comprises admixing the isolated monoclonal \*antibody\* with a pharmaceutical carrier. \*Treating\* a subject comprises administering to them a composition of (4). Specifically, \*treating\* SARS comprises administering an amount of an \*antibody\* or \*antibody\* fragment of (3) to a patient. Preventing transmission of the SARS virus comprises administering an amount of an \*antibody\* or \*antibody\* fragment of (3) to a patient. Diagnosing SARS

comprises contacting an \*antibody\* or \*antibody\* fragment of (3) with a sample. Activating human B memory lymphocytes comprises contacting the lymphocytes with a polyclonal B cell activator. Preparing a recombinant cell...

... preparing an immortalized B cell clone by the method described above; (b) obtaining and/or sequencing nucleic acid from the B cell clone encoding an \*antibody\* of interest; and (c) using the sequence information from step (b) to prepare nucleic acid for inserting into an expression host to permit expression of the \*antibody\* of interest in that host. The expression host is a eukaryotic cell, e.g. a yeast cell, an animal cell or a plant cell. The...

... a human cell. The human cell is a PER. C6 cell or a HKB-11 cell.

Preparing and obtaining a nucleic acid molecule encoding an \*antibody\* of interest comprises preparing an immortalized B cell clone by the method described above, and obtaining and/or sequencing from the B cell clone nucleic acid encoding the \*antibody\* of interest. Preparing an \*antibody\* for pharmaceutical use comprises selecting an immortalized B cell that produces an \*antibody\* with a desired specificity, obtaining and/or sequencing nucleic acid from the selected B cell the \*antibody\* of interest, inserting the nucleic acid into or using the nucleic acid to prepare an expression host that can express the \*antibody\* of interest, culturing or sub-culturing the expression host under conditions where the \*antibody\* of interest is expressed, and optionally, purifying the \*antibody\* of the interest. The nucleic acid is manipulated between steps (b) and (c) to introduce restriction sites, to change codon usage, and/or to add or optimize transcription and/or translation regulatory sequences. Preferred \*Antibody\*: The \*antibody\* fragment is an Fv, a Fab or an F(ab')<sub>2</sub>. Preferred Composition: The composition comprises two or more of the monoclonal \*antibody\* and/or fragment, where the two or more recognize either (i) different epitopes of the same antigen, or (ii) different antigens. ACTIVITY - Antimicrobial; Cytostatic; Antiinflammatory; Immunosuppressive. No biological data given. MECHANISM OF ACTION - Gene Therapy. USE - The monoclonal \*antibody\* or \*antibody\* fragment is useful in manufacturing a medicament for \*treatment\* of a patient, e.g. a patient with SARS, for diagnosing a disease, or as a medicament (claimed). The method is useful for producing a clone of an immortalized human B memory lymphocyte capable of producing a human monoclonal \*antibody\* with a desired antigen specificity. The immortalized B cell clone, \*antibodies\*, composition, and methods are useful for diagnosing, \*treating\*, and preventing infectious diseases, cancers, inflammatory diseases, autoimmune diseases, allergic diseases, or SARS. ADMINISTRATION - Dosage is 0.01-50, preferably 0.05-10 mg/kg

...  
DESCRIPTORS: recombinant vector-mediated gene transfer, expression in host cell, monoclonal \*antibody\*, Fab, appl., infectious disease, \*cancer\*, inflammatory disease, autoimmune disease, allergy prevention, diagnosis, gene therapy \*antibody\* (23, 43)

SECTION: PHARMACEUTICALS-\*Antibodies\*-...

...GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques and Analysis; DISEASE-\*Cancer\*-...

...DISEASE-Other Diseases; DIAGNOSTICS-\*Antibody\*-Based Diagnostics



DIALOG(R)File 357:Derwent Biotech Res.  
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0344369 DBR Accession No.: 2004-16661 PATENT

**New recombinant human monoclonal \*antibody\* that specifically binds to  
\*Tumor\* Necrosis Factor-alpha, useful for \*treating\* neoplastic disease  
such as cancers, or immuno-mediated inflammatory diseases such as  
rheumatoid arthritis - \*antibody\* production against \*tumor\* necrosis  
factor via cell culture for use in disease therapy**

AUTHOR: BABCOOK J S; KANG J S; FOORD O; GREEN L; FENG X; KLAKAMP S;  
HAAK-FRENDSCHO M; RATHANASWAMI P; PIGOTT C; LIANG M L; LEE R;  
MANCHULENCHO K; FAGGIONI R; SENALDI G; QIAOJUAN J S

PATENT ASSIGNEE: ABGENIX INC 2004

PATENT NUMBER: WO 200450683 PATENT DATE: 20040617 WPI ACCESSION NO.:  
2004-480601 (200445)

PRIORITY APPLIC. NO.: US 430729 APPLIC. DATE: 20021202

NATIONAL APPLIC. NO.: WO 2003US38281 APPLIC. DATE: 20031202

LANGUAGE: English

**New recombinant human monoclonal \*antibody\* that specifically binds to  
\*Tumor\* Necrosis Factor-alpha, useful for \*treating\* neoplastic disease  
such as cancers, or immuno-mediated inflammatory diseases such as  
rheumatoid arthritis - \*antibody\* production against \*tumor\* necrosis  
factor via cell culture for use in disease therapy**

ABSTRACT: DERWENT ABSTRACT: NOVELTY - A human monoclonal \*antibody\* (I)  
that specifically binds to \*Tumor\* Necrosis Factor-alpha (TNFa) and  
comprises: (a) a heavy chain complementarity determining region 1  
(CDR1) having the two fully defined 5 amino acid sequence (S1...

... as Arg-Ala-Ser-Gln-Ser-Val-Ser-Ser-Asn-Leu-Ala. INDEPENDENT CLAIMS are  
included for the following: (1) assaying (M1) the level of \*tumor\*  
necrosis factor alpha (TNFa) in a patient sample, comprising contacting  
with (I), and detecting the level of binding between the \*antibody\* and  
TNFa in the sample; (2) a composition comprising the \*antibody\* or its  
functional fragment and a carrier; (3) \*treating\* (M2) an animal  
suffering from a neoplastic, or an immuno-mediated inflammatory disease  
by selecting an animal in need of \*treatment\* for the disease; and  
administering of the fully human monoclonal \*antibody\* of (I); and (4)  
inhibiting (M3) TNFa induced apoptosis in an animal by selecting an  
animal in need of \*treatment\* for TNFa induced apoptosis; and  
administering the fully human monoclonal \*antibody\* of (I).  
BIOTECHNOLOGY - Preferred \*Antibody\*: Where (I) comprises (S1), the  
\*antibody\* preferably comprises: (a) a heavy chain CDR2 sequence of:  
Val-Ile-Trp-Ser-Asp-Gly-Ser-Ile-Lys-Tyr-Tyr-Ala-Asp-Ser-Val-Lys...

... comprising the fully defined 107 amino acid sequence (SEQ ID NO: 72)  
given in the specification. Where (I) comprises the heavy chain of  
(S2), the \*antibody\* preferably comprises: (a) a heavy chain CDR2  
sequence of: Val-Ile-Tyr-Ser-Gly-Asp-Arg-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-Ly  
s-Gly...

... light chain CDR1, CDR2 and CDR3 correspond to canonical class 2, 1 and  
3, respectively. Preferred Method: In (M1), the biological sample is  
blood. In \*treating\* an animal suffering from a neoplastic disease, the  
neoplastic disease is selected from breast \*cancer\*, ovarian \*cancer\*,  
bladder \*cancer\*, lung \*cancer\*, glioblastoma, stomach \*cancer\*,  
endometrial \*cancer\*, kidney \*cancer\*, colon \*cancer\*, pancreatic  
\*cancer\*, and prostate \*cancer\*. ACTIVITY - Anabolic;  
Antiarteriosclerotic; Antiarthritic; Antibacterial; Antiinflammatory;

Antipsoriatic; Antirheumatic; Eating-Disorders-Gen.; Immunomodulator; Immunosuppressive; Nephrotropic; Neuroprotective; Vasotropic; Antiapoptotic. No biological data given. MECHANISM OF ACTION - TNF alpha antagonist. The ability of the anti-human TNFa \*antibodies\* to neutralize TNFa in vivo to protect hepatic injury induced by TNFa was studied in 8-10 weeks old Balb/c female mice. Inhibition (IC50s) compared to known monoclonal \*antibodies\* was 50 nM and 48 nM for the inventive \*antibodies\* compared to 41, 40 and 27 nM for Infliximab, Adalimumab and Etanercept, respectively. USE - The \*antibody\* is useful in the preparation of medicament for \*treating\* TNF induced apoptosis, neoplastic disease such as breast \*cancer\*, ovarian \*cancer\*, bladder \*cancer\*, lung \*cancer\*, glioblastoma, stomach \*cancer\*, endometrial \*cancer\*, kidney \*cancer\*, colon \*cancer\*, pancreatic \*cancer\*, and prostate \*cancer\* ; or immuno-mediated inflammatory diseases such as rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn's disease, graft-host reactions, septic shock, cachexia, anorexia...

...0.001-100 mg/kg. Administration is infusion or injection by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intrathecal, inhalation, or intralesional routes. EXAMPLE - Human monoclonal \*antibodies\* against human TNFa were developed by sequentially immunizing XENOMOUSE (RTM). To generate hybridomas, cohorts of XMG2L3 and 3B-L3 XENOMOUSE (RTM) mice were immunized with TNFa alone or TNFa with \*CPG\* via foot pad. The initial immunization was with 10 microg of antigen mixed with 1:1 v/v with TITERMAX GOLD (RTM) per mouse. A...

... mouse. The mRNA for the heavy and light chains were isolated and transcribed into cDNA before transfection into kidney 293 cells to produce recombinant monoclonal \*antibodies\*. (213 pages)

DESCRIPTORS: \*tumor\* necrosis factor, monoclonal \*antibody\*, hybridoma cell culture, heavy, light chain, appl. neoplastic, mamma, ovary, bladder, lung, glioblastoma, stomach, endometrial, kidney, colon, pancreas, prostate \*cancer\*, immuno-mediated inflammatory disease, rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, restenosis, autoimmune disease, Crohn disease, graft-host reaction, septic shock, cachexia, anorexia, multiple sclerosis therapy lymphokine antitumor \*cytokine\* protein \*tumor\* anabolic antiarteriosclerotic antirheumatic antiinflammatory antipsoriatic immunomodulator immunosuppressive nephrotropic neuroprotective vasotropic DNA sequence protein sequence (23, 35)

SECTION: PHARMACEUTICALS-\*Antibodies\*--...

...BIOMANUFACTURING and BIOCATALYSIS-Animal/Plant Cell Culture; DISEASE-\*Cancer\*--

7/3,K/20 (Item 8 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0332891 DBR Accession No.: 2004-05183 PATENT

**New fusion partner protein, useful in medicine, or in manufacturing an immunogenic composition for eliciting an immune response in a patient or \*treating\* a patient suffering from or susceptible to \*cancer\* or infectious diseases - recombinant protein production via plasmid expression in host cell for use in vaccine**

AUTHOR: CABEZON SILIVA T E V; ELLIS J H; GERARD C M G; HAMBLIN P A;

PALMANTIER R M; VINALS Y DE BASSOLS C  
PATENT ASSIGNEE: GLAXOSMITHKLINE BIOLOGICALS SA; GLAXO GROUP LTD 2003  
PATENT NUMBER: WO 2003104272 PATENT DATE: 20031218 WPI ACCESSION NO.:  
2004-062310 (2004)  
PRIORITY APPLIC. NO.: GB 2003914 APPLIC. DATE: 20030115  
NATIONAL APPLIC. NO.: WO 2003EP6096 APPLIC. DATE: 20030606  
LANGUAGE: English

**New fusion partner protein, useful in medicine, or in manufacturing an immunogenic composition for eliciting an immune response in a patient or \*treating\* a patient suffering from or susceptible to \*cancer\* or infectious diseases - recombinant protein production via plasmid expression in host cell for use in vaccine**

...ABSTRACT: culturing the host cell under conditions sufficient for the production of the fusion protein, and recovering the fusion protein from the culture medium; and (7) \*treating\* a patient suffering from \*cancer\* by administering the immunogenic composition. BIOTECHNOLOGY - Preferred Fusion Protein: The choline binding domain is derived from the C terminus of LytA. The C-LytA or...

... epidermidis, Borrelia spp., Chlamydia spp., including Chlamydia trachomatis, Chlamydia pneumoniae, Plasmodium spp., including Plasmodium falciparum, Toxoplasma spp., or Candida spp.. The heterologous protein is a \*tumor\* associated protein or tissue specific protein, or its immunogenic fragment. The heterologous protein or its fragment is MAGE 1, MAGE 3, MAGE 4, PRAME, BAGE...

... Immunogenic Composition: The immunogenic composition additionally comprises a T helper-1 inducing adjuvant, e.g. 3D-MPL, QS21, a mixture of QS21 and cholesterol, a \*CpG\* oligonucleotide, or a mixture of two or more of the adjuvants. The DNA sequence is coated onto biodegradable beads or delivered via a particle bombardment...

...with 10 microg of the CPC-P501S protein formulated in different adjuvant systems. The serology (total immunoglobulin response) and cellular response (T cell lymphoproliferation and \*cytokine\* production) were analyzed on spleen cells, 6-14 days after the last vaccination. The adjuvanted CPC-P501S proteins gave a good \*antibody\* response after vaccination. A P501 specific lymphoproliferation was seen in the spleen of all groups of mice receiving the adjuvanted protein after in vitro re...

...response in a patient by sequential administration of the protein followed by the DNA sequence, or the DNA sequence followed by the protein, or for \*treating\* a patient suffering from or susceptible to \*cancer\*, e.g. prostate \*cancer\*, colorectal \*cancer\*, lung \*cancer\*, breast \*cancer\* or melanoma (all claimed). The immunogenic composition is also useful for \*treating\* infectious diseases. ADMINISTRATION - Administration of the composition is intramuscularly, subcutaneously, intraperitoneally, or intravenously. No dosage details given. EXAMPLE - The P2 sequence of tetanus toxin was...

... pRIT15199 was obtained. PCR amplification was performed using the plasmid as template and the oligonucleotides C-lytANOTATG and C-lytA-aa55. The amplified fragment was \*treated\* with the restriction enzymes NcoI and Afl III to generate the cohesive ends. The fragment was ligated with vector pRIT15068 to generate the complete fusion...

DESCRIPTORS: ...fusion protein prep., choline binding domain, heterologous promiscuous T-helper epitope, vector-mediated gene transfer expression

in host cell, appl. immunogenic composition, infectious disease,  
melanoma, \*cancer\* therapy, recombinant vaccine \*tumor\* cytostatic DNA  
sequence (23, 10)  
...SECTION: GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques  
and Analysis; DISEASE-\*Cancer\*-

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DIALOG(R)File 357:Derwent Biotech Res.  
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Diagnosing a colon cell proliferative disorder in a subject comprises  
obtaining one or more samples from colon tissue or serum the subject,  
and detecting a decrease in the amount or expression of a polypeptide  
expressed from the EYA4 gene - EYA4 protein expression decreasing  
determination for use in disease therapy and gene therapy

AUTHOR: ADORJAN P; BURGER M; MAIER S; LESCHE R; COTTRELL S; DE VOS T

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LANGUAGE: English

...ABSTRACT: the following: (1) repressing transformation in a colon cell  
by contacting the cell with an EYA4 polypeptide to inhibit a  
transformed phenotype; (2) preventing or \*treating\* a colon cell  
proliferative disorder in a subject by administering to the subject a  
compound that agonizes EYA4; (3) a nucleic acid comprising a sequence...

...Preferred Method: In diagnosing a colon cell proliferative disorder, the  
colon cell proliferative disorders are taken from the group comprising  
adenocarcinomas, squamous cell cancers, carcinoid \*tumors\*, sarcomas,  
and lymphomas. The detection is by immunoassay, in particular by an  
ELISA. The immunoassay is a radioimmunoassay. Alternatively, the method  
comprises obtaining one or more test samples from colon tissue or serum  
or both of the subject; contacting the sample with an \*antibody\*  
immunoreactive with the EYA4 polypeptide to form an immunocomplex;  
detecting the immunocomplex; comparing the quantity of the  
immunocomplex to the quantity of immunocomplex formed under identical  
conditions with the same \*antibody\* and a control sample from one or  
more subjects known not to have colon \*cancer\*, where a decrease in  
quantity of the immunocomplex in the sample from the subject relative  
to the control sample is indicative of colon \*cancer\* . The  
immunocomplex is detected in a Western blot assay, preferably in an  
ELISA. The detection is by expression analysis. The method comprises  
detecting the presence...

... encoding polynucleotide further comprises control sequences operatively  
linked to the EYA4 encoding polynucleotide. The EYA4-encoding  
polynucleotide is present in a vector. In preventing or \*treating\* a  
colon cell proliferative disorder in a subject, the detection comprises  
methylation analysis of the gene EYA 4, its promoter and/or regulatory  
elements, in...

... sequence as cited above. Detecting, differentiating or distinguishing  
between colon cell proliferative disorders comprises obtaining, from a  
subject, a biological sample having subject genomic DNA; \*treating\* the

#### VIRAL FACTORS IN THE PATHOGENESIS OF LUNG \*CANCER\*

There is no evidence yet that HIV infection leads to an increased incidence of lung \*cancer\*. However, lung \*tumors\* arising in HIV-positive patients with or without the acquired immunodeficiency syndrome (AIDS) have a severalfold increase in the frequency of microsatellite alterations, which indicates increased genetic instability (160).

Lung \*cancer\* is the leading cause of \*cancer\* death in Taiwanese women, although less than 10[percent] of female lung \*cancer\* patients are smokers, which suggests that other factors are important for developing lung \*cancer\* (161). A recent study indicated that human papillomavirus (HPV) oncogenic subtypes 16/18 may be involved in the pathogenesis of lung \*cancer\* of these Taiwanese women (161). Fifty-five percent of lung \*tumor\* patients had HPV 16/18 DNA compared with 27[percent] of noncancer control subjects, which had undergone thoracic surgery for lung diseases other than \*cancer\*. Also the odds ratio ([similar]10-fold) of HPV16/18 infection of nonsmoking female lung \*cancer\* patients was much higher compared with nonsmoking male lung \*cancer\* patients (odds ratio of [similar]2). Additionally, HPV 16/18 DNA was uniformly located in lung \*tumor\* cells, but not in the adjacent noninvolved lung. These results strongly suggest that HPV infection with virus subtypes known to be oncogenic for cervical \*cancer\* is associated with lung \*cancer\* development of nonsmoking Taiwanese female lung \*cancer\* patients. Because oncogenic HPV subtypes encode E6 and E7 viral oncoproteins, which inactivate p53 and Rb protein, respectively, HPV infection provides several key mutations at...

...inactivation of key TSG proteins (166). Although SV40 is definitely involved in the pathogenesis of mesotheliomas, it does not appear to be involved in lung \*cancer\* pathogenesis.

Jaagsiekte sheep retrovirus (JSRV) can induce rapid, multifocal lung \*cancer\* in sheep, but JSRV is a simple retrovirus having no known oncogenes so the mechanism of oncogenesis is still unknown. Recently, HYAL2, a glycosylphosphatidylinositol...

...JSRV (167). Of great interest is the fact that the HYAL2 gene resides in the 600-kb 3p21.3 TSG homozygous deletion region (55). Lung \*cancer\* induced by JSRV closely resembles human bronchiolo-alveolar carcinoma. Further studies are necessary to investigate the relationship of JSRV oncogenesis to human bronchiolo-alveolar carcinoma.

#### SECOND PRIMARY LUNG CANCERS

The risk of developing a second lung \*cancer\* in patients who survived resection of NSCLC is approximately 1-2[percent] per patient per year (168). The average risk of developing a second lung \*cancer\* in patients who survived SCLC is approximately 6[percent] per patient per year (168). Because of the high risk of developing a second lung \*cancer\*, these patients need to be followed carefully for many years. This increased risk probably represents a persistent field defect in the respiratory epithelium of patients cured of one lung \*cancer\*. This defect probably involves the multiple somatically acquired genetic changes detected in respiratory epithelium described previously that predispose these individuals to lung \*cancer\* development. In a related scenario, molecular changes including p53 and KRAS mutations and analysis of LOH and microsatellite alterations at nine chromosomal regions were investigated...although future research is necessary to address the possible contribution of these alterations to the pathogenesis of second primary lung cancers.

#### PROGNOSTIC MARKERS IN LUNG \*CANCER\*

A recent study (170) investigated a panel of nine molecular markers

including p53, Bcl-2, ErbB-2 (HER-2/neu), KI-67, RB, EGFR, factor...  
 ...RB, CD-44, and factor VIII were of prognostic significance. Sabel et al.  
 (171) reported a negative impact of CD40 expression on survival of lung  
 \*cancer\* patients. Cyclin E is a G1 cyclin and one of the key regulators of  
 the G1-S transition. The expression of cyclin E was investigated by  
 immunohistochemistry in a large series of NSCLCs (172). High-cylin E  
 expression was found more frequently in \*tumors\* from smokers than from  
 nonsmokers, in squamous cell carcinomas than in nonsquamous carcinomas, and  
 in later-stage (pT2-4) \*tumors\* than in early-stage (pT1) \*tumors\*.  
 Additionally, patients whose \*tumors\* showed high-level cyclin E expression  
 survived a significantly shorter time than patients with \*tumors\* having  
 low-level expression. However, other CDK2-associated cyclins, including  
 cyclin E2, cyclin A1, and cyclin A2, do not have a prognostic role in NSCLC  
 (173).

#### CONCLUSIONS

The understanding of lung \*cancer\* pathogenesis has grown rapidly over the  
 recent years, but our knowledge will grow even more in the next decade with  
 the information from the Human...

...Project. The use of techniques such as microarrays for testing  
 expression of nearly all human genes and their isoforms at the same time  
 in lung \*cancer\*, or other genome-wide strategies involving proteomics,  
 will provide large amounts of information that need to be translated into  
 clinical practice and integrated into our understanding of lung \*cancer\*  
 pathogenesis. The main goals for future studies should focus on how this  
 information can be used in terms of risk assessment, prevention, early  
 detection of lung \*cancer\*, and development of new therapeutic targets. New  
 \*treatment\* strategies including drugs that block oncogene functions such  
 as tyrosine kinase inhibitors, gene therapy, monoclonal \*antibodies\*  
 against growth factors and receptors, angiogenesis inhibitors, vaccines,  
 apoptosis modulators, demethylating agents, and new drugs targeted at  
 abnormal pathways are being developed and introduced into clinical trials.  
 These approaches should help to decrease the number of lung \*cancer\* deaths  
 through early detection and \*treatment\* and increase the cure and prolong  
 the survival of patients with lung \*cancer\*.

#### Added material

Sabine Zochbauer-Muller<sup>1</sup>, Adi F. Gazdar<sup>1,2</sup>, and John D. Minna<sup>1,3,4</sup>  
<sup>1</sup> Hamon Center for Therapeutic Oncology Research, Departments of 2...

...UTSouthwestern.edu; John.Minna@UTSouthwestern.edu

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TABLE 1 Major molecular abnormalities in the pathogenesis of lung  
 \*cancer\*

#### FOOTNOTE

a Frequent allele loss at chromosomal sites 1p13, 1p36, 3p14-cen,  
 3p21.3-22, 3p25-26, 4p15.1-15.3, 4q25-26, 4q33-34...

...8	ND	
GSTP1	7-9	ND
BRCA1	4	ND

p73	0	ND
hMLH1	0	ND
p15	0	ND

#### FOOTNOTES

a Most SCLC data are from \*tumor\* cell lines because of the clinical difficulty in getting pretreatment \*tumor\* samples for study. ND, not done; NSCLC, non-small cell lung \*cancer\*; SCLC, small cell lung \*cancer\*; APC, adenomatous polyposis coli; CDH13, H-cadherin; RARb, retinoic acid receptor b-2; FHIT, fragile histidine triad; TIMP-3, tissue inhibitor of metalloproteinase-3; p16, p16INK4a; MGMT, O6-methylguanine-DNA methyltransferase; DAPK, death-associated protein kinase; ECAD, E-cadherin; GSTP1, glutathione-S-transferase P1; p14, p14ARF; p15, p15INK4b. Data \*extracted\* from references 56-58, 63, 74, 105-107, 120, 122-126.

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DESCRIPTORS:

...\*Cancer\*

7/3,K/9 (Item 1 from file: 135)

DIALOG(R)File 135:NewsRx Weekly Reports

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0000067507 (USE FORMAT 7 OR 9 FOR FULLTEXT)

**Patent issued covering novel CpG oligonucleotides**

Biotech Week, October 2, 2002, p.52

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English

RECORD TYPE: FULLTEXT

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TEXT: Hybridon, Inc., (HYBN.OB) announced the issuance of U.S. Patent No. 6,426,334 claiming a novel class of CpG oligonucleotides for the \*treatment\* of \*cancer\*.

"The issuance of this patent makes Hybridon a leader in creating second-generation CpG Immunomodulatory Oligonucleotides (IMO)," said James B. Wyngaarden, MD, Hybridon's chairman...

The patent, entitled "Oligonucleotide Mediated Specific \*Cytokine\* Induction and Reduction of \*Tumor\* Growth in a Mammal," covers a method for using \*CpG\* oligonucleotides containing four contiguous guanosines for reducing \*tumor\* growth in mammals. These oligonucleotides induce various \*cytokines\*, including interleukin-12 and interferons. The inventors of the patent are Sudhir Agrawal, D.Phil., Hybridon's president and chief scientific officer, and Qiuyan Zhao...

...compounds that mimic bacterial DNA that activate the human immune system to fight diseases. Independent reports have shown that CpG oligonucleotides are useful in the \*treatment\* of \*cancer\*, infectious diseases, and asthma/allergies, either alone or in combination with antigens, \*antibodies\*, or conventional therapies.

This article was prepared by Biotech Week editors from staff and other



reports.

7/3,K/10 (Item 1 from file: 144)  
DIALOG(R) File 144:Pascal  
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16689323 PASCAL No.: 04-0341947  
**Hypomethylation of DNA and the insulin-like growth factor-II gene in dichloroacetic and trichloroacetic acid-promoted mouse liver \*tumors\***  
LIANHUI TAO; YINGZHE LI; KRAMER Paula M; WEI WANG; PEREIRA Michael A  
Department of Pathology, Medical College of Ohio, 3055 Arlington Avenue,  
Toledo, OH 43614-5806, United States  
Journal: Toxicology : (Amsterdam), 2004, 196 (1-2) 127-136  
Language: English

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**Hypomethylation of DNA and the insulin-like growth factor-II gene in dichloroacetic and trichloroacetic acid-promoted mouse liver \*tumors\***  
Dichloroacetic acid (DCA) and trichloroacetic acid (TCA) are mouse liver carcinogens. DNA hypomethylation is a common molecular event in \*cancer\* that is induced by DCA and TCA. Hypomethylation of DNA and the insulin-like growth factor-II (IGF-II) gene was determined in DCA- and TCA-promoted liver \*tumors\*. Mouse liver \*tumors\* were initiated by N-methyl-N-nitrosourea and promoted by either DCA or TCA. By dot-blot analysis using an \*antibody\* for 5-methylcytosine, the DNA in DCA- and TCA-promoted \*tumors\* was demonstrated to be hypomethylated. The methylation status of 28 \*CpG\* sites in the differentially methylated region-2 (DMR-2) of mouse IGF-II gene was determined. In liver, 79.3 +/- 1.7% of the sites were methylated, while in DCA- and TCA-\*treated\* mice, only 46.4 +/- 2.1% and 58.0 +/- 1.7% of them were methylated and 8.7 +/- 2.6% and 10.7 +/- 7.4% were methylated in \*tumors\*. The decreased methylation found in liver from mice exposed to DCA or TCA occurred only in the upstream region of DMR-2, while in \*tumors\* it occurred throughout the probed region. mRNA expression of the IGF-II gene was increased in DCA- and TCA-promoted liver \*tumors\* but not in non-involved liver from DCA- and TCA-exposed mice. The results support the hypothesis that DNA hypomethylation is involved in the mechanism for the \*tumorigenicity\* of DCA and TCA.

English Descriptors: Methylation; DNA; Insulin like growth factor; Gene; Genetics; Animal; Mouse; Liver; \*Tumor\*; \*Cytokine\*; Messenger RNA

French Descriptors: Methylation; DNA; Facteur croissance IGF; Gene; Genetique; Animal; Souris; Foie; Tumeur; \*Cytokine\*; RNA messenger

Spanish Descriptors: Metilacion; DNA; Factor crecimiento IGF; Gen; Genetica; Animal; Raton; Higado; \*Tumor\*; Citoquina; RNA mensajero

7/3,K/11 (Item 1 from file: 266)  
DIALOG(R) File 266:FEDRIP  
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00592792  
IDENTIFYING NO.: 5R01CA104804-02 AGENCY CODE: CRISP  
**Rational Design of Therapeutic Vaccines for CEA+ \*Tumors\***  
PRINCIPAL INVESTIGATOR: CHATTERJEE, MALAYA B

ADDRESS: MALAYA.CHATTERJEE@UC.EDU UNIVERSITY OF CINCINNATI P O BOX 670508  
CINCINNATI, OH 45267

PERFORMING ORG.: UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

DATES: 2009/30/03 TO 2008/31/08 FY : 2004

**Rational Design of Therapeutic Vaccines for CEA+ \*Tumors\***

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

SUMMARY: DESCRIPTION (provided by applicant): Extensive preclinical studies, as well as results obtained from clinical trials, suggest that vaccination with an anti-idiotypic (Id) \*antibody\* (3H1) that mimics an epitope of human carcinoembryonic antigen (CEA) has the potential to augment survival benefits. Anti-Id 3H1 breaks immune tolerance to CEA and induces anti-CEA \*antibody\* as well as CD4+T helper (Th1) responses in colorectal \*cancer\* patients and also in mice transgenic for CEA. This anti-Id approach in its current form, although promising, will need improvements to realize its full potential. Suitable murine \*tumor\* models will be used to explore strategies that will significantly improve the therapeutic impact of this vaccine. The proposal is based on the hypothesis that...

... T-help, in the host, will provide critical help for priming and activation of CEA-specific CTL, the major effector cells (CD8+ T cells) for \*tumor\* destruction. We hypothesize that the combination of CD4+ with CD8+ T cell epitopes will further augment the anti-\*tumor\* immune responses. The specific aims of this proposal are: 1) to determine whether vaccination with 3H1, which will generate anti-CEA Ab and T-help, in combination with mRNA derived from CEA, using dendritic cells (DC) as APC, will induce CTL and engender therapeutic immunity in an established \*tumor\* model in C57BL/6 mice (H2kb), double transgenic for human CEA and HLA-A2; 2) to explore whether a combination of 3H1 with HLA-A2 restricted known agonist CTL epitopes of CEA, using DC as APC, will work better in the above \*tumor\* model; 3) to test whether the idio-peptides, (LCD-2 and CEA-B) derived from the structure of 3H1 and CEA based on the amino...

... the agonist CTL peptides of CEA. The criteria for selection of the optimal regimen for vaccination will be based on the ability to invoke anti-\*tumor\* activities in vitro and in vivo. We will measure the \*antibody\* titer, in vitro CTL activity, intra-cellular \*cytokine\* levels and in vivo \*tumor\* regression. In Aim 4, we will further explore methods to boost \*tumor\*-specific CD4+ as well as CD8+ T cell responses in vivo by coadministration of agents such as IL-2, IL-12, \*CpG\* ODN or anti-CTLA4 \*antibody\*. We will test for any possible autoimmune responses in CEA-expressing normal organs of mice by histopathological analysis (Aim 5). Promising strategies indicated by these...

... in Aim 6 in the murine Apc knock-out transgenic mice expressing CEA and HLA-A2, which arguably, are the best murine model for colon \*cancer\*, as it closely resembles the human disease. The results obtained from these studies will help design improved therapeutic vaccines for the \*treatment\* of CEA+ \*tumors\* and can be incorporated readily into our ongoing clinical programs.

DESCRIPTORS: laboratory mouse; immune tolerance /unresponsiveness; anti-idiotypic \*antibody\*; carcinoembryonal antigen; neoplasm /\*cancer\* immunotherapy; colon neoplasm; nonhuman therapy evaluation; neoplasm / \*cancer\* vaccine; vaccine development

DIALOG(R) File 266:FEDRIP

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IDENTIFYING NO.: 5R01CA083856-04 AGENCY CODE: CRISP

**NOVEL STRATEGIES FOR THE IMMUNOTHERAPY OF COLON \*CANCER\***

PRINCIPAL INVESTIGATOR: REISFELD, RALPH A

ADDRESS: reisfeld@scripps.edu DEPARTMENT OF IMMUNOLOGY ROOM 218 IMM-13 LA JOLLA, CA 92037

PERFORMING ORG.: SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

DATES: 2005/08/00 TO 2004/30/05 FY : 2003

**NOVEL STRATEGIES FOR THE IMMUNOTHERAPY OF COLON \*CANCER\***

SPONSORING ORG.: NATIONAL \*CANCER\* INSTITUTE

...SUMMARY: human CEA-based DNA vaccines for the effective immunotherapy of colon carcinoma. The investigators will test the hypothesis that peripheral T cell tolerance to these \*tumor\* self-antigens can be overcome by DNA vaccines boosted by effective adjuvants designed to generate cytolytic T lymphocyte (CTLs) specific for CEA epitopes expressed as...

... either transgenic for CEA or double transgenic for CEA and HLA-A2.1Kb. Their aim is to use such models for optimization of vaccine by \*antibody\*-  
\*cytokine\* fusion proteins and to investigate basic concepts such as mechanisms of T cell co-stimulation, generation of \*tumor\*-specific CTLs and T memory cells and establish principles for adoptive immunotherapy. The specific aims designed to achieve these objectives are: 1) construction of optimal...

... a string of beads or direct targeting of single CEA or repeat epitopes to the endoplasmic reticulum; 3) achievement of optimal adjuvant activity using either unmethylated \*CpG\* dinucleotide motifs or CD40 Ligand/Trimer co-expression; and 4) determination whether \*antibody\*-IL2 fusion proteins can effectively boost DNA vaccines to achieve optimal, long-lived \*tumor\*-protective immunity, as well as eradicate established metastases, and identification of immunological mechanisms involved in generating \*tumor\*-specific CTLs and T memory cells. The achievement of this proposal's objectives should lead to the design of effective DNA vaccines based on rational immunological principles that may ultimately lead to the improved \*treatment\* of colon \*cancer\*.

DESCRIPTORS: laboratory mouse; genetically modified animal; Listeria; Salmonella typhimurium; cytotoxic T lymphocyte; passive immunization; antigen presentation; carcinoembryonal antigen; disease /disorder model; neoplasm /\*cancer\* immunotherapy; neoplasm /\*cancer\* immunology; colon neoplasm; ubiquitin; chimeric protein; nonhuman therapy evaluation; neoplasm /\*cancer\* vaccine; proteasome; vaccine development; vector vaccine

7/3,K/13 (Item 1 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0364877 DBR Accession No.: 2005-10581 PATENT

**Modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection by providing a host cell with a thioaptamer that modifies the activity of a DNA-binding protein involved in an immune response - involving vector-mediated gene transfer and expression in host cell for therapy**

AUTHOR: GORENSTEIN D G; LUXON B A; HERZOG N; ARONSON J F; BEASLEY D;

BARRET A; SHOPE R E; YANG X B  
PATENT ASSIGNEE: UNIV TEXAS SYSTEM 2005  
PATENT NUMBER: WO 200518537 PATENT DATE: 20050303 WPI ACCESSION NO.:  
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LANGUAGE: English

**Modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection by providing a host cell with a thioaptamer that modifies the activity of a DNA-binding protein involved in an...**

...ABSTRACT: a transcription factor involved in T cell activation where at least a portion of at least one nucleotide is thiophosphate-modified; (6) a method of \*treating\* a hemorrhagic viral infection; (7) a method of \*treating\* a neuropathologic viral infection; and (8) a method for enhancing vaccine efficacy. BIOTECHNOLOGY - Preferred Method: Modifying an immune response comprises providing a host cell with...

...cell immune response. The modification of the immune response is a shift in a Th1 to Th2 ratio. The immune response is to bacteria, fungus, \*cancer\*, self-antigen, heterologous antigen, retrovirus, hemorrhagic virus or neuropathologic virus. The immune response is in vivo. The thioaptamer modifies \*antibody\* production or cytotoxic T cell activation. Modifying an immune response comprises administering to a host a composition comprising an antigen and one or more partially...

... protein. The composition further comprises IL-1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12 or 13, Type I Interferon, Type II Interferon, \*tumor\* necrosis factor alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), lymphotoxin migration inhibition factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte-macrophage CSF...

... immunity activator. The helper T cell response is in vivo. The helper T cell response comprises a T helper 1-type or 2-type response. \*Treating\* a hemorrhagic viral infection comprises identifying a patient suspected of being infected with a hemorrhagic virus and providing the patient with a therapeutic amount of...

... Ebola virus, Marburg virus, yellow fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus, Rift Valley fever virus or Congo-Crimean hemorrhagic fever virus. \*Treating\* a neuropathologic viral infection comprises identifying a patient suspected of being infected with a neuropathologic virus and providing the patient with a therapeutic amount of...

... DNA binding protein and an antigen. The method further comprises a carrier molecule, comprising liposomes, microcapsules and/or microspheres. The immune response is to a \*cancer\*, allergic rhinitis, eczema, urticaria, anaphylaxis, transplant rejection, systemic lupus erythematosus, rheumatoid arthritis, seronegative spondyloarthritides, Sjogren's syndrome, systemic sclerosis, polymyositis, dermatomyositis, Type I Diabetes Mellitus, Acquired Immune Deficiency Syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, polyendocrine autoimmune disease, hepatitis, sclerosing cholangitis, primary biliary cirrhosis, pernicious anemia, celiac disease, \*antibody\*-mediated nephritis, glomerulonephritis, Wegener's granulomatosis, microscopic polyarteritis, polyarteritis nodosa, pemphigus, dermatitis herpetiformis, psoriasis, vitiligo, multiple sclerosis, encephalomyelitis, Guillain-Barre syndrome, Myasthenia

Gravis, Lambert-Eaton...

- ... of the thioaptamer is thio-modified. The vaccine comprises one or more pharmaceutically acceptable salts. The antigen comprises a virus, a bacterium, a fungus, a \*cancer\*, a self-antigen, a heterologous antigen, a retrovirus, a hemorrhagic virus or a neuropathologic virus. The antigen comprises a West Nile Virus. The vaccine is...
  - ... or dissolved form. The antigen comprises a live-attenuated or heat-inactivated antigen. The antigen comprises a pathogen-associated molecular pattern antigen, which is a \*CpG\* molecule or polysaccharide. The thioaptamer comprises a concatenated aptamer comprising one or more concatenated thioaptamers. The protein that the thioaptamer binds specifically with comprises a...
  - ... receptor 2 or 4. **ACTIVITY** - Virucide. No biological data given. **MECHANISM OF ACTION** - Vaccine. **USE** - The method is useful in modifying an immune response for \*treating\* hemorrhagic or neuropathologic viral infection (claimed). **ADMINISTRATION** - The composition is administered via oral or parenteral route (claimed). No dosage given. (72 pages)
- DESCRIPTORS:** recombinant interferon, \*tumor\* necrosis factor, granulocyte-macrophage colony stimulating factor, vascular endothelial cell growth factor prep., isol., vector-mediated gene transfer, expression in host cell, aptamer, appl., hemorrhagic disorder, neuropathologic virus infection therapy, recombinant vaccine prep. virucide antitumor immunostimulant protein lymphokine \*cytokine\* leukocyte (24, 16)

7/3,K/14 (Item 2 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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**Detecting/detecting and distinguishing between or among prostate cell proliferative disorders or their stages in a subject, useful for \*treating\* prostate \*cancer\*, by determining gene expression level of e.g. supervillin (SVIL) - involving vector-mediated gene transfer and expression in host cell for gene therapy**

**AUTHOR:** VANAJA D K; YOUNG C Y F

**PATENT ASSIGNEE:** MAYO FOUND MEDICAL EDUCATION and RES 2005

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**PRIORITY APPLIC. NO.:** US 487553 **APPLIC. DATE:** 20030714

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**LANGUAGE:** English

**Detecting/detecting and distinguishing between or among prostate cell proliferative disorders or their stages in a subject, useful for \*treating\* prostate \*cancer\*, by determining gene expression level of e.g. supervillin (SVIL) - involving vector-mediated gene transfer and expression in host cell for gene therapy**

...**ABSTRACT:** among prostate cell proliferative disorders or their stages is, at least in part, afforded. **INDEPENDENT CLAIMS** are also included for the following: (1) an isolated \*treated\* nucleic acid derived from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treatment\* is to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of

hybridization; (2) a nucleic acid, comprising at least 16 contiguous nucleotides of a \*treated\* genomic DNA sequence derived from a sequence selected from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treatment\* is to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine...

... hybridize under high stringency to them. The polypeptide is detected by at least one method selected from immunoassay, Enzyme-Linked Immunosorbent Assay immunoassay, radioimmunoassay, and \*antibody\*. The expression is determined by detecting the presence or absence of \*CpG\* methylation within the gene or sequence, where hypermethylation indicates the presence of, or stage of the prostate cell proliferative disorder. Expression is of at least...

... DNA; and contacting genomic DNA obtained from the subject with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated \*CpG\* dinucleotides within at least one target region of the genomic DNA, where the target region comprises, or hybridizes under stringent conditions to at least 16...

... 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the contiguous nucleotides comprise at least one \*CpG\* dinucleotide sequence, and where detecting, or detecting and distinguishing between or among colon cell proliferative disorders or stages is, at least in part, afforded. Normal...

... intermediate, T2, Gleason score 6 lymph node positive and negative; high grade, T3, Gleason score 9 lymph node positive and negative; prostatic adenocarcinoma; and metastatic \*tumors\*. Adjacent benign tissue is distinguished from at least one condition selected from intermediate, T2, Gleason score 6 lymph node positive and negative; high grade, T3, Gleason score 9 lymph node positive and negative; prostatic adenocarcinoma; and metastatic \*tumors\*, and where the target region comprises, or hybridizes under stringent conditions to at least 16 contiguous nucleotides of a sequence selected from ZNF185 (SEQ ID...

... subject, a biological sample having genomic DNA; contacting the genomic DNA, or its fragment, with one reagent(s) that distinguishes between methylated and non methylated \*CpG\* dinucleotide sequences within at least one target sequence of the genomic DNA, or its fragment, where the target sequence comprises, or hybridizes under stringent conditions ...

... 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, the contiguous nucleotides comprising at least one \*CpG\* dinucleotide sequence; and determining, based at least in part on the distinguishing, the methylation state of at least one target \*CpG\* dinucleotide sequence, or an average, or a value reflecting an average methylation state of target \*CpG\* dinucleotide sequences, where detecting, or detecting and distinguishing between or among prostate cell proliferative disorders or stages thereof is, at least in part, afforded. Detecting...

... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. Distinguishing between methylated and non methylated \*CpG\* dinucleotide sequences within the target sequence comprises converting unmethylated cytosine bases within

the target sequence to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties. Distinguishing between methylated and non-methylated \*CpG\* dinucleotide sequences within the target sequence(s) comprises methylation state-dependent conversion or non-conversion of at least one \*CpG\* dinucleotide sequence to the corresponding converted or non-converted dinucleotide sequence. The biological sample is selected from cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, ejaculate, urine, blood, and their combinations. Distinguishing between methylated and non methylated \*CpG\* dinucleotide sequences within the target sequence comprises use of at least one nucleic acid molecule or peptide nucleic acid (PNA) molecule comprising, in each case...

- ... 1, 29, 31,32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements. The contiguous sequence comprises at least one \*CpG\*, TpG or CpA dinucleotide sequence. The method comprises use of at least two such nucleic acid molecules, or PNA molecules. The method comprises use of...
- ... use of at least four such nucleic acid molecules, PNA molecules. The method may comprise obtaining, from a subject, a biological sample having genomic DNA; \*extracting\* or otherwise isolating the genomic DNA; \*treating\* the genomic DNA, or its fragment, with one or more reagents to convert cytosine bases that are unmethylated in the 5-position thereof to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties; contacting the \*treated\* genomic DNA, or the \*treated\* fragment, with an amplification enzyme and at least two primers comprising, in each case a contiguous sequence of at least 9 nucleotides that is complementary  
...
- ...selected from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, where the \*treated\* genomic DNA or its fragment is either amplified to produce at least one amplificate, or is not amplified; and determining, based on a presence or absence of, or on a property of the amplificate, the methylation state of at least one \*CpG\* dinucleotide of a sequence selected from SEQ ID NOs: 1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51, and their complements, or an average, or a value reflecting an average methylation state of the \*CpG\* dinucleotides, where at least one of detecting, and detecting and distinguishing between prostate cell proliferative disorders or stages is, at least in part, afforded. \*Treating\* the genomic DNA, or its fragment comprises use of a reagent selected from bisulfite, hydrogen sulfite, disulfite, and their combinations. Contacting or amplifying comprises use...
- ... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. The method further comprises for the step of contacting the \*treated\* genomic DNA, the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least...
- ... the amplificate. Contacting or amplifying comprises use of methylation-specific primers. The method comprises, for the contacting step, using primer oligonucleotides comprising one or more \*CpG\*; TpG or CpA dinucleotides; and further comprising, for the determining step, the use of at least one method selected from hybridizing in at least one...

- ... base; and sequencing, in the determining step, of the amplificate. The method comprises, in the contacting step, amplification by primer oligonucleotides comprising one or more \*CpG\*; TpG or CpA dinucleotides and further comprising, in the determining step, hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at...
- ... or hybridizes under stringent conditions to a bisulfite-converted sequence derived. The method may comprise obtaining, from a subject, a biological sample having genomic DNA; \*extracting\* , or otherwise isolating the genomic DNA; contacting the genomic DNA, or its fragment, comprising at least 16 contiguous nucleotides of a sequence selected from SEQ...
- ... determining, based on a presence or absence of, or on property of at least one such cleavage fragment, the methylation state of at least one \*CpG\* dinucleotide of a sequence selected from SEQ ID NOs:1, 29, 31, 32, 34, 35, 37, 38, 40, 42, 43, 45, 47, 49, 51; and their complements, or an average, or a value reflecting an average methylation state of \*CpG\* dinucleotides, where at least one of detecting, or of detecting and differentiating between or among prostate cell proliferative disorders or stages is, at least in...
- ... from cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, ejaculate, urine, blood, and their combinations. The contiguous base sequence comprises at least one \*CpG\*, TpG or CpA dinucleotide sequence. The \*treatment\* comprises use of a reagent selected from bisulfite, hydrogen sulfite, disulfite, and their combinations. The method comprises use of the kit above. Preferred Oligomer: The oligomer comprises at least one \*CpG\*, CpA or TpG dinucleotide sequence. Preferred Array: The oligomers are bound to a planar solid phase in the form of a lattice selected from linear...
- ... of oligonucleotides is useful for at least one of detection of; detection and differentiation between or among subclasses or stages of; diagnosis of; prognosis of; \*treatment\* of; monitoring of; and \*treatment\* and monitoring of prostate cell proliferative disorders. The nucleic acid, an oligonucleotide or a set of oligonucleotides is useful for detecting, or detecting and distinguishing...
- ... Gleason score 6 lymph node positive or negative tissue; high grade, T3, Gleason score 9 lymph node positive or negative tissue; prostatic adenocarcinoma; and metastatic \*tumors\*. The set of oligomers is useful as probes for determining at least one of a cytosine methylation state, and a single nucleotide polymorphism (SNP) of...
- ... oligonucleotides, method of manufacturing, array and kit is useful for detecting, detecting and differentiating between or among subclasses or stages of, diagnosis of, prognosis of, \*treatment\* of, monitoring of, or \*treatment\* and monitoring of prostate cell proliferative disorders (all claimed). The method is useful for improved diagnosis, \*treatment\* and monitoring of prostate cell proliferative disorders, more specifically by enabling the improved identification of and differentiation between subclasses of the disorder or stages of prostate \*tumors\*. ADMINISTRATION - Dosage is 0.01-50 mg/kg body weight via parenteral injection e.g., subcutaneously, intraperitoneally, intravenously or intramuscularly, myocardial, intratumoral, peritumoral, or to the interstitial space of a tissue. EXAMPLE - Total RNA was \*extracted\* from 30 frozen prostate tissue section with Trizol (RTM) r